BlueCross BlueShield of Kansas City

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Olysio (simeprivir)

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Policy

BCBSKC will provide coverage for Olysio (simeprivir) when it is determined to be medically necessary because the following criteria have been met.

When Policy Topic is covered

Coverage of Olysio is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Chronic Hepatitis C (CHC) Genotype 1 – Adults.** Approve Olysio for 12 weeks in patients that meet the all of following criteria (a, b, c, and d):
   - **a)** The patient is ≥ 18 years of age; AND
   - **b)** The patient does not have recurrent hepatitis C virus (HCV) following liver transplantation (see Criteria 2); AND
   - **c)** Olysio is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
   - **d)** The patient meets ONE of the following conditions (i or ii):
     - **i.** Olysio will be prescribed **in combination with PR**: Approve if the patient does not have genotype 1a AND the Q80K polymorphism. (Note: testing for the Q80K polymorphism is not required for patients with genotype 1b); OR
     - **ii.** Olysio will be prescribed **in combination with Sovaldi**[14] (Note: this is not an FDA-approved use): Approve if the patient meets ONE of the following conditions (1 or 2):
       - **(1)** The patient is treatment-naïve or a prior relapser AND the patient is interferon ineligible meaning they meet ONE of the following conditions: documented intolerance to interferon, autoimmune hepatitis, other autoimmune disorders; hypersensitivity to peginterferon or any of its components; decompensated hepatic disease, history of depression, or clinical features consistent with depression, baseline neutrophil count < 1,500 cells/µL, baseline platelet count < 90,000 cells/µL, baseline hemoglobin < 10 g/dL; or preexisting cardiac disease; OR
       - **(2)** The patient is a prior non-responder (prior null or partial response) to PR.

Note: The duration of therapy with Olysio should not exceed 12 weeks.

Olysio is indicated in combination with PR for the treatment of adults with genotype 1 CHC.[1] The efficacy of Olysio in combination with PR is substantially reduced in patients infected with genotype 1a CHC with a NS3 Q80K polymorphism at baseline compared with patients infected with HCV genotype 1a without the Q80K polymorphism. Screening patients with genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.

In combination with PR, the recommended duration of therapy for all patients is 12 weeks unless on-treatment viral stopping rules are met.[1] The turnaround time for HCV RNA testing varies and

may be up to 2 weeks. To prevent treatment failure, the dose of Olysio must not be reduced or interrupted.

Olysio for 12 weeks in combination with PR for 24 weeks in an alternative regimen in treatment-naïve patients who are eligible to receive and have genotype 1b CHC or genotype 1a CHC without the Q80K polymorphism (Class IIa, Level A) according to the AASLD/IDSA guidance.[14] In prior null or partial responders, Olysio for 12 weeks in combination with PR for 48 weeks is an alternative regimen for interferon eligible adults with genotype 1 CHC (Class IIa, Level A). The combination of Olysio and Sovaldi ± ribavirin for 12 weeks is recommended in treatment-naïve/relapse interferon ineligible adults with genotype 1 CHC (Class I, Level A) as well as in prior PR (without protease inhibitor for HCV) non-responders (prior null or partial response) with genotype 1 CHC regardless of interferon eligibility or HCV genotype subtype (Class IIa, Level B).

The efficacy of Sovaldi in combination with Olysio is under investigation as part of the COSMOS trial (see *Combination Use with Sovaldi* above for study details). Among patient who had viral relapse, Olysio resistance-associated variants have been observed; Sovaldi resistance associated variants have not been detected.[14] For patients with genotype 1a HCV, baseline resistance testing for the Q80K polymorphism may be considered. However, in contrast to using Olysio to treat a genotype 1a patients with PR when the mutation significantly alters the probability of an SVR, the finding of the Q80K polymorphism does not preclude treatment with Olysio and Sovaldi, because the SVR rate was high in patients with genotype 1a/Q80K infection (SVR12 in cohort 1 was 86% [n = 24/28]; SVR4 for cohort 2 was 90% [n = 10/11]). To date virologic failure has not been observed in patients in either cohort infected with HCV genotype 1b and with genotype 1a in the absence of Q80K. Thus Q80K testing can be considered but is not strongly recommended for combination use of Sovaldi with Olysio. This regimen should be considered only in those patients who require immediate treatment, since it is anticipated that safer and more effective interferon-free regimens will be available by 2015.

In the opinion of a specialist physician reviewing the data we have adopted the criteria for combination use with Sovaldi and Olysio.

Other Uses with Supportive Evidence

2. **Recurrent HCV Post-Liver Transplantation – Adults.** Approve Olysio for 12 weeks in patients who meet all of the following criteria (a, b, c, d, and e):
   - **a)** The patient is ≥ 18 years of age; AND
   - **b)** The patient has genotype 1 recurrent HCV after a liver transplantation; AND
   - **c)** Olysio is prescribed by or in consultation with one of the following prescribers who is affiliated with a liver transplant center[14]: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
   - **d)** The patient has not been previously treated for their *recurrent* HCV post transplant; AND
   - **e)** Olysio is prescribed in combination with Sovaldi.

   The AASLD/IDSA recommend Sovaldi with Olysio ± ribavirin for 12 to 24 weeks in patients with genotype 1 in the allograft liver, including those with compensated cirrhosis (Class IIb, Level C).[14] The alternative regimen for treatment-naïve patients with genotype 1 HCV in the allograft liver is Sovaldi with ribavirin with or without peginterferon for 24 weeks (Class IIb, Level C).

   The combination of Olysio and Sovaldi have not been studied in the post-transplant setting; however,
   drug interaction studies in non-infected participans indicated that Olysio can be used safely in conjunction with calcineurin inhibitors.[14] Based on these data, the guidance notes that clinicians may consider the use of Sovaldi with Olysio as described for non-transplant patients, particularly those expected to have difficulty tolerating ribavirin (e.g., patients with impaired renal function and

anemia). Consideration should be given to pretreatment resistance testing for the Q80K polymorphism in genotype 1a infected patients.

In the opinion of a specialist physician reviewing the data we have adopted this criterion.

3. **Patient Has Been Started on Olysio.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications) or other use with supportive evidence to complete a course of therapy. Authorization for Olysio should not exceed 12 weeks of therapy. For example if a patient is eligible for 12 weeks of therapy and has received 3 weeks of therapy, approve 9 weeks of therapy to complete the 12-week course.

When Policy Topic is not covered

Coverage of Olysio is recommended in circumstances that are listed in the Recommended Authorization Criteria (FDA-Approved Indications and Other Uses with Supportive Evidence). The following provides rationale for specific Exclusions. This is not an exhaustive list of Exclusions.

1. **CHC, Non-Genotype 1.** The safety and efficacy of Olysio in patients with non-genotype 1 CHC have not been established. Olysio is indicated for patients with genotype 1 CHC infection.[1] There is an ongoing study assessing the efficacy of Olysio in treatment-naïve and treatment-experienced patients with genotype 4 CHC, no efficacy data are available.[12] Sovaldi is the recommended therapy for patients with genotype 4 CHC according to the AASLD/IDSA guidance. The AASLD/IDSA guidance recommends Sovaldi PR for 12 weeks in treatment-naïve/relapse, interferon eligible patients with genotype 4 CHC (Class IIa, Level B).[14] Olysio for 12 weeks is an alternative regimen provided for treatment-naïve patients with genotype 4 CHC who are interferon eligible in combination with PR for 24 to 48 weeks (Class IIb, Level B). In Genotype 4 non-responder patients, the AASLD/IDSA guidance recommends Sovaldi PR for 12 weeks in interferon eligible patients (Class IIa, Level C). The alternate regimen for patients with genotype 4 who are prior non-responders is Sovaldi R for 24 weeks (Class IIa, Level B).

   The Phase III RESTORE trial (unpublished) assessed the safety and efficacy of Olysio PR in treatment-naïve or treatment-experienced patients with genotype 4 CHC (n = 107).[15] Among the patients with Week 24 data available in the interim analysis (n = 30), 97% of patients (n = 29/30) had achieved an HCV RNA < 25 IU/mL undetectable at Week 24. Among patients who met criteria for shortened therapy, 91% of patients have achieved SVR4 (n = 10/11) and 100% have achieved SVR 12 (n = 3/3).[14] Therapy has failed in four patients: three patients had detectable virus at the end of treatment and one experienced virologic relapse. A Phase IIa study assessed the pharmacokinetics of Olysio 200 mg QD (the FDA-approved dose is 150 mg QD) administered for 7 days in treatment-naïve patients with genotypes 2 to 6 CHC (n = 37).[15] The mean plasma HCV RNA change from baseline for patients with genotype 4 CHC at Day 8 (primary endpoint) was -3.52 $\log_{10}$.

   In the opinion of a specialist physician reviewing the data we have adopted this criterion.

2. **CHC, Genotype 1a with Q80K Polymorphism or Q80K Polymorphism Status Unknown, Unless Olysio is Prescribed in Combination with Sovaldi (see Criteria 1ii and 2).** The efficacy of Olysio in combination with PR is substantially reduced in patients infected with genotype 1a CHC with an NS3 Q80K polymorphism at baseline compared to patients infected with HCV genotype 1a without the Q80K polymorphism.[1] Screening patients with genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism. However, in contrast to using Olysio to treat a genotype 1a patients with PR when the mutation significantly alters the probability of an SVR, the finding of the Q80K polymorphism does not preclude treatment with Olysio and Sovaldi.[14] To date virologic failure has not been observed in patients in either cohort of the COSMOS trial infected with HCV genotype 1b

and with genotype 1a in the absence of Q80K. Thus Q80K testing can be considered but is not strongly recommended for combination use of Sovaldi with Olysio.

3. **Monotherapy with Olysio.** Olysio must not be used as monotherapy.[1,14]

4. **Pediatric Patients (age < 18 years).** The safety and efficacy of Olysio have not been established in pediatric patients. Olysio is indicated for use in *adult* patients with genotype 1 chronic HCV.[1] Guidelines from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Practice (NASPGHAN) for the diagnosis and management of hepatitis C infection in infants, children, and adolescents state that the protease inhibitors (Victrelis and Incivek) should only be used in children in the context of a clinical trial as they have not been studied in children nor are there published pharmacokinetic or safety data in the pediatric population.[13] In the opinion of a specialist physician reviewing the data we have adopted this criterion.

5. **Patient Has Failed Therapy with Olysio or Another NS3/4A Protease Inhibitor for HCV (i.e., Incivek or Victrelis). [Note: this does not include patients who have discontinued Incivek or Victrelis due to an adverse reaction to Incivek or Victrelis. Failure includes prior null response, partial response, or relapse]** The efficacy of Olysio has not been studied in patients who have previously failed therapy with a treatment regimen that includes Olysio or other HCV protease inhibitors.[1] Olysio is an alternative regimen for patients who have had a prior non-response (null response, partial response, or relapse) to PR only (not to triple therapy with a protease inhibitor and PR).

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Considerations

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Hayes Medical Technology Directory, Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service

Overview

Olysio is a hepatitis C virus (HCV) non-serine 3/4A (NS3/4A) protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen with peginterferon and ribavirin (PR).[1] The efficacy of Olysio PR has been established in patients with genotype 1 CHC with compensated liver disease, including cirrhosis. The following points should be considered when initiating Olysio for treatment of CHC:

- Olysio must not be used as monotherapy;
- The efficacy of Olysio in combination with PR is influenced by baseline host factors;
- The efficacy of Olysio in combination with PR is substantially reduced in patients infected with genotype 1a CHC with an NS3 Q80K polymorphism at baseline compared with patients infected with HCV genotype 1a without the Q80K polymorphism. Screening patients with genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism; and
- The efficacy of Olysio has not been studied in patients who have previously failed therapy with a treatment regimen that includes Olysio or other HCV protease inhibitors (i.e., Incivek® [telaprevir tablets] and Victrelis® [boceprevir capsules]).

Olysio represents the third NS3/4A protease inhibitor indicated in patients with genotype 1 CHC. There are no data directly comparing the clinical efficacy of Olysio with the other NS3/4A protease inhibitors.

However, efficacy (sustained virologic response [SVR]) has been established in treatment-naïve adults with genotype 1 CHC as well as prior treatment-failure (null responders and partial responders) and relapse patients.[2-6]

Rationale

Dosing

Olysio Food and Drug Administration (FDA)-approved for once-daily dosing administered in combination with PR (as triple therapy) for 12 weeks.[1] To prevent treatment failure, the dose of Olysio must not be reduced or interrupted. In all patients, treatment with Olysio should be initiated in combination with PR and should be administered for 12 weeks. All *treatment-naïve* and *prior relapse patients*, including those with cirrhosis, should receive an additional 12 weeks of PR after completing 12 weeks of triple-therapy with Olysio PR (total treatment duration of 24 weeks). All *prior non-responder patients* (including partial and null responders), including those with cirrhosis, should received an additional 36 weeks of PR after completing 12 weeks of treatment with Olysio PR (total duration of treatment 48 weeks). The recommended duration of treatment with Olysio PR is also presented in Table 1.

Table 1. Duration of Treatment with Olysio PR.[1]

	Duration of Treatment with Olysio PR*	Duration of Treatment with PR*	Total Treatment Duration*
Treatment-naïve and prior relapser† patients including those with cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior non-responder (partial and null responders)‡ including those with cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks

PR – Peginterferon alfa and ribavirin; * Recommended duration of treatment if the patient does not meet stopping rules (see Table 2); † Prior relapser defined as a patient with undetectable hepatitis C virus (HCV) RNA at the end of prior interferon-based therapy and detectable HCV RNA during follow-up; ‡ Prior partial responder is defined as prior on-treatment ≥ 2 $\log_{10}$ IU/mL reduction in HCV RNA from baseline at Week 12 and detectable HCV RNA at the end of prior interferon-based therapy. Prior null responder is defined as prior on-treatment < 2 $\log_{10}$ reduction in HCV RNA from baseline at Week 12 during prior interferon-based therapy.

It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients.[1] If peginterferon alfa or ribavirin are discontinued for any reason, Olysio must also be discontinued. If treatment with Olysio is discontinued because of adverse reactions or inadequate on-treatment virologic response, Olysio treatment must not be reinitiated. Table 2 contains guidance for treatment stopping rules. HCV RNA levels should be monitored as clinically indicated. Use of a sensitive assay with a lower limit of quantification of at least 25 IU/mL for monitoring is recommended.

Table 2. Treatment Stopping Rules in Any Patient with Inadequate On-Treatment Virologic Response.[1]

HCV RNA	Action
TW 4: ≥ 25 IU/mL	Discontinue Olysio and PR
TW 12: ≥ 25 IU/mL	Discontinue PR (treatment with Olysio is complete at Week 12).
TW 24: ≥ 25 IU/mL	Discontinue PR

HCV – Hepatitis C virus; TW – Treatment week; PR – Peginterferon alfa and ribavirin.

Q80K Polymorphism

In the pooled analysis of the Phase III trials QUEST-1, QUEST-2, and PROMISE, the efficacy of Olysio in combination with PR was substantially reduced in patients infected with HCV genotype 1a with the NS3 Q80K polymorphism at baseline.[1] Culture studies have indicated that Q80K expression was

associated with an approximately 10-fold decrease in the susceptibility of HCV to Olysio relative to wild-type controls.[7] The difference was noted in both of the pooled treatment-naïve studies and the relapser study (SVR rates of 84% vs. 43%, respectively [treatment-naïve] and 78% vs. 24%, respectively [relapse study]).[14] The overall SVR in the subgroup of patients with baseline Q80K polymorphism was no better than that in the placebo group. Although in prior non-responder patients (including null, partial, and relapse patients) in the Phase IIb ASPIRE[6] trial SVR rates did not differ between patients with and without the Q80K polymorphism, prescribing information still supports the use of the test prior to initiating Olysio and does not support use in patients with the polymorphism.[1] If used in combination with Sovaldi, baseline resistance testing for the Q80K polymorphism may be considered in patients with genotype 1a HCV.[14] However, in contrast to using Olysio to treat genotype 1a patients with PR where the mutation significantly alters the probability of an SVR, the finding of the Q80K polymorphism does not preclude treatment with Olysio and Sovaldi, because the SVR rate was high in patients with genotype 1a/Q80K infection (see *Combination Use with Sovaldi*). Thus Q80K testing can be considered but is not strongly recommended for combination use of Sovaldi with Olysio.

The Q80K polymorphism is a common polymorphism found in patients with Genotype 1a in the US.[7] In an analysis pooling patients from the Phase III and Phase IIb trials with Olysio, of the 298 patients with CHC genotype 1a from the US with sequencing data, 48% had the Q80K polymorphism at baseline. None of the genotype 1b patients in the US with sequencing data had the Q80K polymorphism at baseline. The observed prevalence of the Q80K polymorphism was 30% in patients with genotype 1a and 0.5% in patients with genotype 1b in the Phase IIb and III trials.[1]

The Division of Anti-viral Products (DAVP) recommends that all genotype 1a patients be screened for the Q80K polymorphism given the high frequency of the Q80K polymorphism in the US population and its significant impact on rates of sustained viral response 12 weeks after the end of treatment (SVR12).[7] Alternative treatment options for patients with this polymorphism should be considered, notably, no Q80K-related reduction in efficacy was observed during the pivotal trials with Incivek or Victrelis. The HCV GenoSure® NS3/4A drug resistance test has been approved to screen for the Q80K polymorphism.[8] It also provides a comprehensive sequence-based analysis of drug resistance for HCV protease inhibitors.

Combination Use with Sovaldi

Olysio is not FDA-approved for combination use with Sovaldi. However, it has been studied in this combination. COSMOS (COmbination of SiMeprevir and Sovaldi in HCV genotype 1 naïve and null responders with METAVIR stage F3 to F4 infected patients), is an unpublished exploratory Phase IIa, randomized, open-label study in the US investigating the efficacy and safety of Sovaldi with Olysio ± ribavirin for 12 or 24 weeks in patients with genotype 1 CHC (compensated liver disease).[10-11] Two cohorts were enrolled. Patients in Cohort 1 (n = 80) had a prior null response to treatment with PR and METAVIR stage F0 to F2. In Cohort 2, patients could be prior null responders or be treatment-naïve and had advanced hepatic fibrosis (F3 to F4) [n = 87]. Patients with HIV or hepatitis B virus (HBV) co-infection were excluded. No prior exposure to DAAs was allowed. Patients were randomized to one of four arms (more patients were assigned to ribavirin-containing arms). Arms 1 and 2 consisted of Olysio 150 mg QD with Sovaldi 400 mg QD for 24 weeks ± weight-based ribavirin (1,000 or 1,200 mg/day administered twice daily [BID]). Arms 3 and 4 consisted of Olysio 150 mg QD with Sovaldi 400 mg QD for 12 weeks ± weight-based ribavirin. A pre-planned safety and efficacy interim analysis of Cohort 1 was conducted when all patients in a 12-week treatment arms (Arms 3 and 4) reached 4 weeks after planned treatment end (SVR4) or discontinued study participation prematurely. The primary endpoint was SVR12 (SVR measured 12 weeks after the planned completion of therapy). The majority of patients in Cohort 1 were male (70%) and Caucasian. The IL28B status of most patients was CT (70%) or TT (24%). HCV genotype 1 subtype was 1a in 78% of patients and the Q80K mutation was present in 50% of patients.[10-11] In Cohort 2, 46% of patients were treatment-naïve and 54% of patients were prior null responders.[11] Genotype 1a was present in 78% of Cohort 2 patients at baseline and the Q80K mutation was present in 40.3% of patients.

Results. Among the 80 patients randomized and treated in Cohort 1, 57 patients had reached the end of treatment and had post-treatment follow-up data available. The rate of rapid virological response (RVR) was higher in ribavirin-containing treatment arms, but the difference did not translate into a difference in end-of-treatment response or SVR rates. Rates of SVR4 (SVR measured 4 weeks after the end of treatment) in the 12-week arms were 96% with ribavirin and 93% without ribavirin. Among the patients in the 12 week arms who achieved SVR8 (SVR measured 8 weeks after the end of treatment), 100% of patients (n = 24/24) who reached post-treatment Week 12 follow up achieved SVR12 and 100% of patients (n = 8/8) who reached post-treatment Week 24 follow-up achieved SVR24. Two patients in the 12 week arms relapsed, one patient had been treated with ribavirin and the other was randomized to a ribavirin-sparing arm. There were 18 patients with a Q80K polymorphism at baseline and 16 of these patients (89%) achieved SVR8. SVR8 was also high among patients with genotype 1a (95%; n = 35/37). Table 4 provides efficacy results for Cohort 1. In Cohort 2, 91% (n = 10/11) and 100% (n = 7/7) of patients with METAVIR F4 had SVR4 in the 12 week groups ± ribavirin, respectively.[11] SVR4 was achieved by 93.3% (n = 14/15) and 100% of patients (n = 7/7) with prior null response in the 12 week Cohort 2 arms ± ribavirin, respectively. No viral breakthrough occurred. To date, three patients in the Cohort 1 and 2 12-week groups ± ribavirin and one patient in the Cohort 1 24-week ribavirin group have relapsed, all within 4 weeks of end of treatment. Eight patients discontinued treatment prematurely for non-virologic reasons: Five patients in Cohort 1, three patients in Cohort 2. The SVR rate was high in patients with genotype 1a/Q80K infection (SVR12 in cohort 1 was 86% [n = 24/28]; SVR4 for cohort 2 was 90% [n = 10/11]). To date virologic failure has not been observed in patients in either cohort infected with HCV genotype 1b and with genotype 1a in the absence of Q80K.

Table 4. Efficacy Results from COSMOS: Cohort 1.[10-11]

	24 weeks		12 weeks	
	Olysio + Sovaldi + R	Olysio + Sovaldi	Olysio + Sovaldi + R	Olysio + Sovaldi
RVR, % (n/N)	81.8% (18/22)	66.7% (10/15)	85.2% (23/27)	57.1% (8/14)
Undetectable end of treatment, % (n/N)	83.3% (10/12)	88.9% (8/9)	100% (27/27)	100% (14/14)
Relapse, n	0	0	1	1
SVR4, % (n/N)	66.7% (4/6)	100% (5/5)	96.3% (26/27)	92.9% (13/14)
SVR8, % (n/N)	66.7% (4/6)	100% (5/5)	96.3% (26/27)	92.9% (13/14)

COSMOS – COmbination of SiMeprevir and Sovaldi in HCV genotype 1 naïve and null responders with METAVIR stage F3 to F4 infected patients; R – Ribavirin; RVR – Rapid viral response (data based on patients with available stat at Week 4); SVR4 – Sustained viral response 4 weeks after planned treatment end; SVR 8 – Sustained viral response 8 weeks after planned treatment end.

Guidelines/Recommendations

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) web-based recommendations for testing, managing, and treating hepatitis C have been updated to include the availability of Olysio.[14] These guidelines will be updated as new information becomes available and should be consulted for the most up-to-date information. The recommendations are based on evidence and reflect the best possible management for a given patient and a given point of disease progression. The recommendations are graded with regard to the level of evidence (I through III) and strength of evidence (A through C). The level of evidence for each patient group varies, as does the strength of the recommendation, and is graded as such. A regimen classified as "recommended" is favored in most patients, a regimen classified as "alternative" is optimal in a particular subset of patients within a category. When treatment is clearly inferior or is deemed to be harmful, it is classified as "not recommended". The guidance is not supported by pharmaceutical companies or other commercial interests. The guidance development process is generally consistent with that used by the International Antiviral Society-USA (IAS-USA). The guidance may recommend off-label use of certain drugs.

Olysio is recommended according to its FDA approved uses. In addition, Olysio is a recommended regimen (off-label) in combination with Sovaldi (sofosbuvir tablets) and is considered as an alternative regimen in patients with genotype 4 CHC. In the guidance, treatment-naïve and relapse patients are considered as one group while prior non-responders (including null and partial responders) are considered as a different group. Unique patient populations are also addressed where treatment recommendations differ from those for the general population. In many patients, it may be advisable according to the guidance, to delay treatment in patients with early stage fibrosis (F0 to F2), because there are highly effective, pangenotypic, DAA combinations in an interferon-free regimen expected in the future. The guidance also provides a definition of interferon ineligible patients. Interferon ineligible patients are defined as follows: intolerance to interferon, autoimmune hepatitis and other autoimmune disorders, hypersensitivity to peginterferon or any of its components, decompensated hepatic disease, history of depression, or clinical features consistent with depression, a baseline neutrophil count < 1,500/μLm a baseline platelet count < 90,000/μL, or baseline hemoglobin < 10 g/dL, or a history of preexisting cardiac disease. The guidance offers options (where indicated) for interferon eligible and interferon ineligible patients.

Of note, Incivek and Victrelis are no longer recommended in patients with genotype 1 CHC due to markedly inferior AE profiles, longer treatment duration, high pill burden, drug-drug interactions, frequency of dosing, intensity of monitoring for continuation and stopping of therapy, and the requirement to be taken with high-fat meals, relative to the preferred and alternative recommendations. Below is a brief summary of the recommendations, further detail can be found within the approval criteria below.

In interferon eligible, treatment-naïve or prior relapse adults with genotype 1 CHC, the combination of Sovaldi and Olysio is recommended ± ribavirin for 12 weeks (Class I, Level B). Olysio is the alternative therapy in interferon eligible adults with genotypes 1 or 4 CHC; the recommended duration is Olysio 12 weeks and PR for 24 weeks in patients with genotype 1b or 1a without the Q80K polymorphism (Class IIb, Level A) and PR 24 to 48 weeks (in combination with Olysio) in patients with Genotype 4 CHC (Class IIb, Level B). In prior non-responders to PR (prior partial or null-reponse), Olysio in combination with Sovaldi ± ribavirin for 12 weeks is a recommended regardless of interferon eligibility (Class IIa, Level B). Olysio for 12 weeks in combination with PR for 48 weeks is an alternative regimen for interferon eligible, prior non-responder patients with genotype 1 CHC (Class IIa, Level A). In treatment-naïve and prior relapse patients with HIV co-infection, who are interferon ineligible, one of the recommended therapies is Sovaldi in combination with Olysio for 12 weeks (± ribavirin) [Class IIa, Level C]. In treatment-naïve and prior relapse patients with HIV co-infection, who are interferon eligible, Olysio for 12 weeks in combination with PR for 24 weeks is an alternative regimen (Class IIa, Level B). In prior PR partial or null responders with HIV and genotype 1 CHC co-infection, Olysio in combination with Sovaldi ± ribavirin for 12 weeks is recommended regardless of interferon eligibility (Class IIa, Level C). For patients with recurrent HCV post liver transplantation, the combination of Sovaldi and Olysio ± ribavirin for 12 to 24 weeks is recommended in patients who have not previously received treatment for their recurrent hepatitis C (Class IIb, Level C).

Table 1. Treatment of HCV in Treatment-naïve and Relapse Patients.[14]

Genotype	Recommended		Alternative		Not Recommended
	Interferon Eligible	Interferon Ineligible	Interferon Eligible	Interferon Ineligible	
1	Sovaldi + PR x 12 weeks (Class I, Level A)	**Sovaldi** + **Olysio** ± R x 12 weeks (Class I, Level B)	**Olysio** + PR x 24 weeks† (Class IIa, Level A)	Sovaldi + R x 24 weeks‡ (Class IIb, Level B)	-PR ± Incivek or Victrelis x 24 to 48 weeks (Class IIb, Level A) -Monotherapy with P, R, or DAA.
2	Sovaldi + R x 12 weeks (Class I, Level A)		None		-PR x 24 weeks (Class IIb, Level A)

					-Monotherapy with P, R, or DAA (Class III, Level A) -Incivek, Victrelis, or Olysio- based regimens (Class III, Level A)
3	Sovaldi + R x 24 weeks (Class I, Level B)		Sovaldi + PR x 12 weeks (Class IIa, Level A)	N/A	-PR x 24 or 48 weeks (Class IIb, Level A) -Monotherapy with P, R, or DAA (Class III, Level A) - Incivek, Victrelis, or Olysio-based regimens (Class III, Level A)
4[α]	Sovaldi + PR x 12 weeks (Class IIa, Level B)	Sovaldi + R x 24 weeks (Class IIb, Level B)	**Olysio** x 12 weeks + PR x 24 or 48 weeks (Class IIb, Level B)	N/A	-PR x 48 weeks (Class IIb, Level A) -Monotherapy with P, R, or DAA (Class III, Level A) -Incivek or Victrelis-based regimens (Class III, Level A)
5/6 [α]	Sovaldi + PR x 12 weeks (Class IIa, Level B)	N/A	PR x 48 weeks (Class IIb, Level A)	N/A	-Monotherapy with P, R, or DAA (Class III, Level A) -Incivek or Victrelis-based regimens (Class III, Level A)

Recommendations are regardless of genotype subtype unless otherwise indicated; HCV – Hepatitis C virus; PR – Peginterferon and ribavirin; R – Ribavirin; [†] Only recommended for patients with genotype 1a *without* the Q80K polymorphism or genotype 1b; [‡] Preliminary data suggest that this regimen may be less effective than Sovaldi + Olysio, especially in patients with cirrhosis; P – Peginterferon; DAA – Direct acting antiviral; NA – Not applicable; [α] Few data are available to help guide decision making in patients infected with genotype 4, 5 or 6 CHC.

Table 2. Treatment of HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders).[14]

Genotype	Prior Treatment History	Recommended		Alternative		Not Recommended
		Interferon Eligible	Interferon Ineligible	Interferon Eligible	Interferon Ineligible	
1	PR only	**Sovaldi** + **Olysio** ± R x 12 weeks (Class IIa, Level B)		**Olysio** x 12 weeks + PR x 48 weeks[€] (Class IIa Level A)	N/A	-PR + Incivek or Victrelis (Class IIb, Level A) - Monotherapy with P, R, or DAA (Class III, Level A) -For non-responder patients with genotype 1 and a history of decompensated
	HCV Protease Inhibitor + PR	N/A		**Sovaldi** x 12 weeks + PR x 12 to 24 weeks (Class IIb, Level C)	N/A	

					cirrhosis (moderate or severe hepatic impairment CTP class B or C), treatment is not indicated because of the risks of P, Victrelis, and Incivek in this population.
2	PR	**Sovaldi** + R x 12 weeks (patients with cirrhosis may benefit from 16 weeks) (Class I, Level A)		**Sovaldi** + PR x 12 Weeks (Class IIa, Level B)	N/A	- PR ± Incivek, Victrelis, or Olysio (Class IIb, Level A) - Monotherapy with P, R, or DAA (Class III, Level A)
3	PR	**Sovaldi** + R x 24 weeks (Class IIa, Level A)		**Sovaldi** + PR x 12 weeks (Class IIa, Level B)	N/A	-PR ± Incivek, Victrelis, Olysio (Class IIb, Level A) -P, R, DAA (Class III, Level A)
4[α]	PR	**Sovaldi** + PR x 12 weeks (Class IIa, Level C)	N/A	**Sovaldi** + R x 24 weeks (Class IIa, Level B)		-PR ± Incivek or Victrelis (Class IIb, Level A) - Monotherapy with P, R, or DAA (Class III, Level A)
5/6 [α]	PR	**Sovaldi** + PR x 12 weeks (Class IIa, Level C)	N/A	None	N/A	-PR ± Incivek or Victrelis (Class IIb, Level A) -Monotherapy with P, R, or DAA (Class III, Level A)

Recommendations are regardless of genotype subtype unless otherwise indicated; HCV – Hepatitis C virus; PR – Peginterferon and ribavirin; R – Ribavirin; PR – Peginterferon and ribavirin; P – Peginterferon; R – Ribavirin; [€] All patients with cirrhosis who are receiving Olysio should have well compensated liver disease; DAA – Direct acting antiviral; CTP – Child Turoctte Pugh; N/A – Not applicable.

Table 3. Treatment of HCV in Unique Patient Populations.[14]

Genotype	Prior Treatment History	Recommended		Alternative		Not Recommended
		Interferon Eligible	Interferon Ineligible	Interferon Eligible	Interferon Ineligible	
HIV Co-Infection						
1	Naïve/Relapse	Sovaldi + PR x 12 weeks (Class I, Level B)	-Sovaldi R x 24 weeks (Class I, Level B) -**Sovaldi + Olysio** ± R x 12 weeks[β] (Class IIa, Level C)	Olysio x 12 Weeks + PR x 24 Weeks[†β] (Class IIa, Level B)	None.	-PR ± Incivek or Victrelis x 24 to 48 weeks (Class IIb, Level A) - Monotherapy with P, R, or DAA (Class III, Level A)
	Partial/Null-Response PR	**Sovaldi** + **Olysio** ± R x 12 weeks[β]		Sovaldi + R x 12 weeks (Class IIb, Level C)	Sovaldi + R x 24 Weeks (Class IIb, Level C)	
	Partial/ Null Response Incivek or Victrelis + PR	Treat as recommended for HCV monoinfected patients.		N/A	N/A	
2	Treatment-naïve	Use the same regimens as are recommended for patients with HCV monoinfection; specifically: Sovaldi + R x 12 weeks (patients who are prior nonresponders and have cirrhosis may benefit from 16 weeks of treatment) (Class I, Level B)		None.	N/A	
	Prior Non-Responder			Sovaldi + PR x 12 Weeks (Class IIa, Level C)	N/A	
3	Treatment-naïve	Use the same regimens as are recommended for patients with HCV monoinfection; Sovaldi + R x 24 weeks (Class I, Level B)		None.	N/A	
	Prior Non-Responder			Sovaldi + PR x 12 weeks (Class IIa, Level C)		
4[α]	Treatment-naïve/ Prior Non-Responder	Treat as recommended for patients with HCV co-infection	N/A	None.	N/A	
5/6 [α]	Treatment-naïve/ Prior Non-Responder	Treat as recommended for patients with HCV co-infection	N/A		N/A	
Recurrent Hepatitis C After Liver Transplantation (Compensated or Decompensated Allograft						

HCV)						
1	Treatment-naive (naïve to treatment post transplant)	**Sovaldi + Olysio** ± R x 12 to 24 weeks (Class IIb, Level C)		Sovaldi + R ± P x 24 weeks (Class IIb, Level C)		-Monotherapy with P, R, or DAA (Class III, Level A) -Incivek or Victrelis-based regimens (Class III, Level A)
2	Treatment-naïve (naïve to treatment post transplant)	Sovaldi + R x 24 weeks (Class IIb, Level C)				

Table 3 (continued). Treatment of HCV in Unique Patient Populations.[14]

Genotype	Prior Treatment History	Recommended		Alternative		Not Recommended
		Interferon Eligible	Interferon Ineligible	Interferon Eligible	Interferon Ineligible	
Recurrent Hepatitis C After Liver Transplantation (Compensated or Decompensated Allograft HCV)						
3	Treatment-naïve (naïve to treatment post transplant)	Sovaldi + Rx 24 weeks (Class IIb, Level C)				

HCV – Hepatitis C virus; HIV – Human immunodeficiency virus; PR – Peginterferon and ribavirin; [β] Olysio should only be used with antiretroviral drugs with which it does not have significant interactions; [†] Only recommended for patients with genotype 1a *without* the Q80K polymorphism or genotype 1b; P – Peginterferon; R – Ribavirin; DAA – Direct acting antiviral; N/A – Not applicable; [α] Recommendations are regardless of genotype subtype unless otherwise indicated; PR – Peginterferon and ribavirin; P – Peginterferon; R – Ribavirin; DAA – Direct acting antiviral; NA – Not applicable; [α] Few data are available to help guide decision making in patients infected with genotype 4, 5 or 6 CHC.

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Billing Coding/Physician Documentation Information

N/A Olysio is considered a pharmacy benefit.

Additional Policy Key Words

Policy Number:

Related Topics

N/A

Policy Implementation/Update Information

09/2013 New policy titled Olysio (simeprivir)
09/2014 Policy reviewed – no changes made