



INLAND EMPIRE HEALTH PLAN

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

Drug: Incivek (telaprevir), Victrelis (boceprevir)

Class: Protease Inhibitors (Anti-hepatic Agents)

Formulary Medication(s): Pegasys and Ribavirin

Effective Date: August 2011

Policy/Criteria:

Medi-Cal/HF/HK:

1. Confirmed diagnosis of Hepatitis C with Genotype 1
2. Must not have decompensated liver, co-infection with HIV/AIDs, or solid organ transplant
3. Must be requested with concurrent therapy of peginterferon and ribavirin (monotherapy will not be approved)
4. Must not have any previous treatment failure of either Protease Inhibitors (ie. Incivek or Victrelis)
5. Restricted to gastroenterologist, infectious disease specialist, or physician specializing in treatment of hepatitis (i.e. hepatologist) due to complicated treatment regimens and monitoring
6. Must have previously failed trial of Peginterferon (Pegasys the preferred product) and Ribavirin (ie. Available for Partial, Relapse, or Null responders)
7. Dosing should follow FDA approved pack insert labeling for dose/duration and HCV viral titer check

Medicare Part D:

1. Same as above

Clinical Evidence:

	Incivek	Victrelis
Availability	375mg Tablets	200mg Capsules
FDA Indication	Tx of chronic Hep C (genotype 1) in adults with compensated liver disease; naïve w/o cirrhosis, partial responder w/o cirrhosis, w/ cirrhosis	Tx of chronic Hep C (genotype 1) in adults with compensated liver disease; naïve w/o cirrhosis, partial responder w/o cirrhosis, w/ cirrhosis
Dosing Schedule	Tx with all 3 is started together. Duration is determined by RNA titer at	Tx is started after 4 weeks of pretreatment with Peg Int + Riba.

	<p>4 & 12 wks. If the RNA titer is > 1000 IU at 4 OR 12 wks discontinue. If detectable at 24 wks discontinue all tx. Dose: 750mg TID</p> <p>Naïve/Relapser:</p> <ul style="list-style-type: none"> • If undetectable at 4 & 12 wks, continue another 12 wks with PEG + Riba (total of 24 wks) • If detectable but < 1000 IU/ml at 4 & 12 wks, continue for another 36 wks of PEG + Riba (total of 48 wks) <p>Partial/Null/Cirrhosis:</p> <ul style="list-style-type: none"> • Treat for 12 wks, then continue for a total of 48 wks 	<p>Dose: 800mg TID</p> <p>Naïve/Partial/Relapser:</p> <ul style="list-style-type: none"> • Duration is determined by RNA titer at 8, 12, & 24 wks. • If non-detectable at 8 & 24 wks discontinue therapy at 28 wks. • If detectable at 8 but not 24 wks, then continue to 36wks. • If poor responder to Peg + Riba during initial 4 wks, continue to 48 wks. • Discontinue all 3 if RNA > 100 IU/ml at 12 wks and still detectable at 24 wks <p>Null/Cirrhosis:</p> <ul style="list-style-type: none"> • Tx with all 3 agents for another 44 wks (48 wks total tx period)
Contraindication s/precautions	Must be used in combination with Peg + Riba; therefore any contraindication to Peg or Riba applies to Protease Inhibitors.	Must be used in combination with Peg + Riba; therefore any contraindication to Peg or Riba applies to Protease Inhibitors.
Drug-Drug Interactions	<p>Inhibitor and substrate of CYP-3A4. Low potential inducer of CYP-2C/3A/1A Inhibitor and substrate of P-Glycoprotein</p> <p>Level 1 – Severe Interactions (sample): Alfuzosin, sildenafil, tadalafil, simvastatin, lovastatin, atorvastatin, midazolam, triazolam</p>	<p>Potent Inhibitor and partial substrate of CYP-3A4/5. Inhibitor and substrate of P-Glycoprotein</p> <p>Level 1 – Severe Interactions (sample): Alfuzosin, carbamazepine, drospirenone, estradiol, simvastatin, lovastatin, phenytoin, midazolam, triazolam</p>
Adverse Events	Anemia, neutropenia, thrombocytopenia, GI, Steven Johnson's syndrome	Anemia, neutropenia, thrombocytopenia, GI

SVR Rate	Peg + Riba	Incivek + Peg + Riba	Victrelis + Peg + Riba
Naïve	37-46%	72-79%	63-67%
Relapse/Partial	15-21%	59-86%	59-67%
Null	~5%	32%	---

* SVR is based on reported data from Phase III clinical trials

	Response	Duration	Victrelis Cost/tx	Peg + Riba Cost/tx	Total Cost/tx

Treatment Naïve	Undetectable at week 8 & 24	Vic: 24 wks Peg+Riba: 28 wks	\$31,671	\$18,900	\$50,571
	Detectable at week 8, but undetectable at week 24	Vic: 32 wks Peg+Riba: 48 wks	\$42,228	\$32,400	\$74,628
Partial / Relapser	Undetectable at week 8 & 24	Vic: 32 wks Peg+Riba: 36 wks	\$42,228	\$24,300	\$66,528
	Detectable at week 8, but undetectable at week 24	Vic: 32 wks Peg+Riba: 48 wks	\$42,228	\$32,400	\$74,628
Null Responder	---	Vic: 44 wks Peg+Riba: 48 wks	\$58,064	\$32,400	\$90,464
Cirrhosis	---	Vic: 44 wks Peg+Riba: 48 wks	\$58,064	\$32,400	\$90,464

*Cost: based on AWP 2011

	Response	Duration	Incivek Cost/tx	Peg + Riba Cost/tx	Total Cost/tx
Treatment Naïve	Undetectable at week 4 & 12	Inc: 12 wks Peg+Riba: 24 wks	\$58,968	\$16,200	\$75,168
	Detectable at week 4 and/or at week 12	Inc: 12 wks Peg+Riba: 48 wks	\$58,968	\$32,400	\$91,368
Relapser	Undetectable at week 4 & 12	Inc: 12 wks Peg+Riba: 24 wks	\$58,968	\$16,200	\$75,168
	Detectable at week 4 and/or at week 12	Inc: 12 wks Peg+Riba: 48 wks	\$58,968	\$32,400	\$91,368
Partial Responder	---	Inc: 12 wks Peg+Riba: 48 wks	\$58,968	\$32,400	\$91,368
Null Responder	---	Inc: 12 wks Peg+Riba: 48 wks	\$58,968	\$32,400	\$91,368
Cirrhosis	---	Inc: 12 wks Peg+Riba: 48 wks	\$58,968	\$32,400	\$91,368

*Cost: based on AWP 2011

	Response	Duration	Peg + Riba	Total Cost/tx
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			Cost/tx	
Treatment Naïve	Undetectable at week 12	Peg+Riba: 48 wks	\$32,400	\$32,400

*Cost: based on AWP 2011

1. Updates to treatment guidelines regarding the newly approved protease inhibitors' (Incivek and Victrelis) place in therapy for Hepatitis C will be released soon according to the American Association for the Study of Liver Diseases website.
2. According to the European Association for the Study of the Liver clinical practice guidelines for the management of hepatitis C, the following potential challenges should be considered when using protease inhibitors for hepatitis C therapy:
 - Rapid emergence of drug resistance in particular in previous non-responder patients, subjects not fully adherent to therapy, and individuals not being able to tolerate optimal doses of peginterferon alpha and ribavirin treatment.
 - More strict and frequent monitoring of serum HCV RNA.
 - Lower response rates to triple therapy in patients with advanced liver fibrosis.
 - Adherence to recommended stopping rules for the antiviral agent and/or the entire treatment regimen.
 - Additional side effects associated with protease inhibitor treatment.
3. The protease inhibitors have shown efficacy over current standards therapy and appear to be effective in naïve and treatment-experienced patients with hepatitis C genotype 1.
4. Protease inhibitors utilize Response Guided Therapy where the duration of treatment is based on early response to therapy.
5. Patients with HIV co-infection, pre-transplant patients with low platelet counts, decompensated liver disease, or renal failure, and liver transplant recipients have yet to be studied utilizing protease inhibitors for hepatitis C.
6. Protease inhibitors must not be used as monotherapy due to development of resistance and should be used in combination with peginterferon alpha and ribavirin.
7. Dose adjustments of protease inhibitors are not recommended as dose reductions may lead to the risk of viral breakthrough.
8. Interferon responsiveness seems to be crucial with direct acting antiviral therapy and development of drug-related mutations might be more likely to occur in those patients who are non-responders to interferon alpha than those who respond to interferon alpha.
9. Poor adherence of protease inhibitors can lead to earlier selection of protease inhibitor-resistant variants and a higher likelihood of treatment failure.
10. Anemia is a class effect of linear protease inhibitors, but is more common with boceprevir compared to telaprevir. Rash and pruritus appear to be more common with telaprevir.
11. A randomized, placebo-controlled, phase III study (SPRINT-2) evaluated the efficacy and safety of boceprevir in combination with peginterferon alpha-2b and ribavirin in treatment naïve patients with chronic hepatitis C genotype 1 (N=1,097). The SVR rates for patients on boceprevir were 63% and 67% (response-guided therapy and 44-week treatment regimen) versus 37% for the control group (48 weeks of peginterferon alpha-2b and ribavirin only). The SVR rates for African America/black patients were 42% and 53% for the boceprevir groups compared to 23% for the control group. Forty four percent of subjects were eligible to complete treatment after 28 weeks if they had persistently undetectable HCV-RNA during weeks 8-24. The most common adverse

events were dysgeusia and anemia in subjects treated with boceprevir. Discontinuation of treatment due to adverse events occurred in 12% and 16% for each boceprevir group compared to 16% for the control group. Erythropoietin was administered to 43% of boceprevir patients with 2% of each treatment group discontinuing therapy.

12. A randomized, double-blind, parallel group, phase III study (RESPOND-2) assessed the efficacy and safety of boceprevir in combination with peginterferon alpha-2b and ribavirin in chronic hepatitis C genotype 1 patients (N=403) who had previously failed standard therapy (relapsed or partial responders). Prior null responders (< 2-log₁₀ decrease in HCV-RNA) from previous treatment by week 12 were not eligible for enrollment. The SVR rates were 59% and 67% (response-guided therapy and 44-week treatment) for patients on boceprevir vs 21% in the control arm (48 weeks of peginterferon alpha-2b and ribavirin only). The SVR rates for African America/black patients were 61% and 53% for boceprevir treated groups compared to 8% in the control group. African America/black patients comprised of 12% (n=49) of the study population. There was a higher incidence of anemia, dysgeusia, rash and dry skin in the groups taking boceprevir compared to the control group.
13. A randomized, placebo-controlled phase III study (ADVANCE) evaluated the efficacy and safety of either 8 or 12 weeks of telaprevir treatment in combination with peginterferon alpha-2a and ribavirin in treatment-naïve patients infected with hepatitis C genotype 1 (N=1,095). SVR rates were 72%, 79% and 46% for the 8 week telaprevir group, 12 week telaprevir group, and control group, respectively. More subjects experienced virologic breakthrough while receiving peginterferon alfa and ribavirin alone, 16% compared to 10% in the 12 week telaprevir group. The most common adverse events were pruritus, nausea, rash, anemia, and diarrhea. The discontinuation rate due to adverse events occurred in 11% of 12 week telaprevir group and 1% in the control group.
14. A randomized, open-label, confirmatory phase III trial (ILLUMINATE) compared the efficacy and safety of a total treatment duration of 24 or 48 weeks with telaprevir in combination with peginterferon alpha-2a and ribavirin in treatment-naïve patients with chronic hepatitis C genotype 1 who achieve eRVR (undetectable HCV RNA at 4 weeks and 12). The overall SVR rate was 74%. In patients who achieved an eRVR, SVR rate of 28 week telaprevir-based therapy was non-inferior to 48 week based therapy (92% vs 88%). The most common adverse events in the telaprevir treatment group were rash (37%) and anemia (39%). Discontinuation of telaprevir due to rash and anemia occurred in 7% and 2% of subjects. Discontinuation of all therapy due to adverse events occurred in 17% of patients.
15. A randomized, double-blind, placebo-controlled phase III study (REALIZE) was conducted to determine the safety, efficacy and tolerability of a regimen of telaprevir and peginterferon alpha/ribavirin with or without a 4-week lead-in period compared with peginterferon alpha/ribavirin alone in previously treated patients with chronic hepatitis C genotype 1. Patients (N=662) were randomly allocated for 48 weeks of antiviral treatment. SVR rates between patients taking telaprevir and peginterferon alpha/ribavirin versus peginterferon alpha/ribavirin alone were 86% vs 22% for prior relapsers, 59% vs 15% for prior partial responders, and 32% vs 5% for prior null responders. There were no significant differences between immediate start group and lead-in telaprevir combination group in SVR rates, on-treatment virologic failure, and relapse rates. Rash, anemia, pruritus, and anorectal sign and symptoms were the most frequent adverse events in telaprevir treated patients. Six percent of telaprevir-treated patients discontinued all study medications compared to 3% in the control group.

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<http://www.aasld.org/aboutus/publicpolicy/Pages/newhepctreatments.aspx>
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