
PRIOR AUTHORIZATION DRUG GUIDELINES

INCIVEK (telaprevir film-coated tablets-Vertex) PA Guidelines

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Date Developed: 10/06/11 by Albert Reeves, MD

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NO LONGER AVAILABLE IN THE U.S.

DESCRIPTION

Telaprevir, is a direct acting antiviral agent (DAA) against hepatitis C virus (HCV).¹ In combination with peginterferon alfa and ribavirin (PR), telaprevir tablets are Food and Drug Administration (FDA)- approved for the treatment of genotype 1 chronic HCV 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.¹ When initiating treatment with telaprevir, the following points should be considered:

- telaprevir must not be administered as monotherapy and must only be prescribed with PR;
- a high proportion of previous null-responders (particularly those with cirrhosis) did not achieve a sustained virologic response (SVR) and had telaprevir resistance-associated substitutions emerge on-treatment with telaprevir/PR; and
- the efficacy of telaprevir in patients who have previously failed therapy with a treatment regimen that includes telaprevir or other HCV NS3/4A protease inhibitors (e.g., boceprevir [Victrelis™]) has not been established.

Telaprevir inhibits the NS3/4A protease, one of four viral enzymes essential for viral replication.¹⁻² Structural proteins are materials used to form new virus particles and non-structural proteins (e.g., viral proteases) play an important role in the replication and assembly of HCV.² Telaprevir has demonstrated activity for and efficacy against HCV genotype 1 infection both *in vitro* and *in vivo*. Although the protease inhibitors have been shown to be potent inhibitors of viral replication, when used as monotherapy, resistance quickly develops.³ Therefore, telaprevir must be administered with PR (telaprevir/PR) to minimize the emergence of viral resistance.¹

In HCV, treatment responses are defined by surrogate virological parameters rather than a clinical endpoint.⁴ Several types of virological responses may occur and are labeled according to their timing *relative to PR treatment*:

- **Rapid virologic response (RVR)** is attainment of HCV RNA < 50 IU/mL at treatment week (TW) 4.
- **Early virologic response (EVR)** is a ≥ 2 log₁₀ reduction or complete absence of serum HCV RNA at TW 12 compared to the baseline level.
- **End-of-treatment response (ETR)** is undetectable HCV RNA at the completion of treatment.
- **SVR** is defined as undetectable HCV RNA at the end of treatment and 24 weeks after completion of therapy. SVR is often regarded as “virological cure”, although hepatocellular carcinoma

(HCC) can occur years later, especially when SVR occurs in the setting of cirrhosis. Historically SVR for genotype 1 patients has been assessed at Week 72 (following a 48 week course of therapy with PR); with telaprevir some patients may be eligible for a shorter duration of therapy based on prior treatment status and on-treatment virologic responses. Therefore SVR is assessed 24 weeks after completion of therapy regardless of when that occurs.

An additional virologic response unique to telaprevir has been used in the clinical development of the drug:

- **Extended RVR** (eRVR) is an undetectable HCV RNA at TW 4 and TW 12. eRVR has been used to predict patients that may benefit from a shorter duration of therapy. For purposes of assessing eRVR, an “undetectable” HCV RNA result is required; a confirmed “detectable but below limit of quantification” HCV RNA result should not be considered equivalent to “undetectable”.¹

CLINICAL EFFICACY

The efficacy and safety of telaprevir in patients with genotype 1 chronic HCV infection were evaluated in two pivotal Phase 3 studies (ADVANCE [treatment-naïve] and REALIZE [retreatment]) and one supplemental Phase 3 study (ILLUMINATE [treatment-naïve]).⁵⁻⁹ In the pivotal studies, telaprevir/PR administered for 12 weeks followed by additional weeks of PR was superior to PR for the proportion of patients achieving SVR. ILLUMINATE provided support for use of response-guided therapy (RGT) in treatment-naïve patients.

In ADVANCE (treatment-naïve), the rate of SVR for telaprevir12/PR and PR was 75% and 44%, respectively (difference for telaprevir from PR 31%; 95% confidence interval [CI]: 24, 38; $P < 0.0001$).⁶ The proportion of patients with relapse was 9% for telaprevir12/PR and 28% for PR (no statistical analysis provided). The duration of PR following telaprevir12/PR was 12 or 36 weeks based on eRVR (treatment duration 24 or 48 weeks, respectively). The proportion of patients with eRVR (and therefore candidates for shorter duration therapy [24 weeks]) was 58% and 8% for telaprevir12/PR and PR, respectively.⁹ Among patients with eRVR, 89% and 97% of telaprevir12/PR and PR-treated patients had SVR. Therefore, eRVR status has a positive predictive value for likelihood of achieving SVR when used to guide treatment decisions for individual patients. Rates of SVR among non-eRVR patients in telaprevir/PR groups were also greater than those in the PR group (52% to 60% vs. 42%, respectively).⁵ Sub-population analyses in Black patients and patients with bridging fibrosis/cirrhosis found that telaprevir had a favorable effect on improving rates of SVR compared with PR (no statistical analyses provided).⁹ In Black patients treated with telaprevir12/PR, the rate of SVR was 62% vs. 25% for PR alone. In patients with bridging fibrosis or cirrhosis, the rate of SVR was 62% for telaprevir12/PR vs. 33% for PR alone.

REALIZE (retreatment) evaluated the efficacy, safety and tolerability of telaprevir/PR (two arms; 4-week PR lead-in and simultaneous start) vs. PR in genotype 1 HCV-infected patients with prior PR treatment failure including non-responders (null- and partial-responders) and relapsers ($n = 662$).⁷ In REALIZE, telaprevir12/PR was followed by 36 weeks of PR for all patients (unless futility stopping rules were met). Telaprevir demonstrated superior efficacy vs. PR in all prior treatment failure populations studied (Table 1).⁴ Relapse rates among prior relapsers and non-responders treated with telaprevir were 7% and 23% to 25%, respectively compared with 65% and 33% for PR, respectively.⁷

Table 1. SVR Results* in Each Treatment Arm for the Three Subgroups Evaluated in the REALIZE Study.^{7,9}

	Relapsers (n = 354)	Non-Responders Overall (n = 308)	Non-Responders	
			Partial Responders (n = 124)	Null Responders (n = 184)
Simultaneous Start (telaprevir12/PR)	83% (121/145)	41% (50/121)	59% (29/49)	29% (21/72)

Lead-in (telaprevir12/PR)	88% (124/141)	41% (51/123)	54% (26/48)	33% (25/75)
Control (PR48)	24% (16/68)	9% (6/64)	15% (4/27)	5% (2/37)

* - All SVR rates were statistically significant when compared with control (P < 0.0001); PR – peginterferon/ribavirin; SVR – sustained virologic response; PR48 – peginterferon/ribavirin for 48 weeks

ILLUMINATE was an open-label, Phase III, non-inferiority, supplemental study to evaluate telaprevir-based therapy in treatment-naïve genotype 1 chronic HCV patients (n = 544).⁸ The objective of this study was to evaluate the differences in SVR when using telaprevir RGT (two regimens of telaprevir12/PR; 24-weeks total duration and 48-weeks total duration) in patients achieving eRVR. The study was designed to rule out inferiority of 24-week vs. 48-week treatment duration. Any patient with HCV RNA > 1,000 IU/mL at TW 4 discontinued *telaprevir*, and continued PR while patients with < 2 log₁₀ reduction in HCV RNA from baseline at TW 12 or detectable HCV RNA at TW 24 to TW 36 were to discontinue *all* therapy. The 24-week telaprevir treatment regimen was non-inferior to the 48-week telaprevir treatment regimen in patients with eRVR, corresponding SVR rates were 92% and 88%, respectively (treatment difference 4.5%; 95% CI = -2.1, 11.1).^{8,10} Overall, 72% of patients achieved RVR and 65% achieved eRVR (*the proportion eligible for shorter duration therapy*).¹⁰ Relapse rates were 8% overall and 6% and 3% in the 24-week and 48-week eRVR treatment groups, respectively.⁹ In a sub-population evaluation, 60% of Black patients treated with telaprevir achieved SVR, and 88% with eRVR achieved SVR in both telaprevir treatment groups. SVR was achieved in 63% of patients with bridging fibrosis or cirrhosis with eRVR; 82% of patients achieved SVR in the 24-week treatment arm and 88% of patients achieved SVR in the 48-week treatment arm.

DURATION OF THERAPY

In all patients, telaprevir/PR is administered for of 12 weeks (unless futility stopping rules are met).¹ The subsequent duration of PR following 12 weeks of telaprevir/PR is based on prior treatment history (treatment-naïve or relapse vs. non-response) and for most treatment-naïve patients, on-treatment virologic response (eRVR or non-eRVR). The total duration of therapy is either 24 or 48 weeks. Any patients with HCV RNA > 1,000 IU/mL at TW 4 or TW 12 should not continue on treatment with telaprevir/PR. In patients with detectable HCV RNA at TW 24, PR is discontinued (Table 4). Tables 2 and 3 describe the duration of treatment for treatment-naïve and prior-relapsers and non-responders, respectively. Of note, treatment-naïve patients *with cirrhosis* and eRVR receive 36 weeks of PR following telaprevir/PR (instead of 12 weeks).¹

Table 2. Recommended Treatment Duration Treatment-naïve and Prior Relapse Patients.¹

HCV RNA	Triple-drug duration (telaprevir/PR)	Dual-drug duration (PR)	Total treatment duration
Undetectable at TW 4 and TW 12 (eRVR).*	12 weeks	12 weeks	24 weeks
Detectable (≤ 1,000 IU/mL) at TW 4 and/or TW 12	12 weeks	36 weeks	48 weeks

HCV – hepatitis C virus; TW – treatment week; PR – peginterferon/Ribavirin; eRVR – extended rapid virologic response; * - Treatment-naïve patients with cirrhosis with eRVR benefit from an additional 36 weeks of PR (48 weeks total).

Table 3. Recommended Treatment Duration Prior Partial-responders and Prior Null-responders.¹

	Triple-drug duration (telaprevir/PR)	Dual-drug duration (PR)	Total treatment duration
All Patients	12 weeks	36 weeks	48 weeks

PR – peginterferon/Ribavirin.

Table 4. Treatment Futility Rules: All Patients.¹

HCV RNA	Action
TW 4 or TW 12: > 1,000 IU/mL	Discontinue telaprevir and PR (telaprevir treatment complete at TW 12).
Week 24: Detectable	Discontinue PR.

HCV – hepatitis C virus ;TW - treatment week; PR – peginterferon/ribavirin

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of telaprevir. The duration of treatment with telaprevir is 12 weeks in all patients.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of telaprevir in combination with peginterferon and ribavirin is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Adult patients with chronic HCV genotype 1 mono-infection.** Approve telaprevir for 12 weeks in patients that meet the following criteria a and b.

- a) Telaprevir is prescribed by or in consultation with a gastroenterologist or infectious disease physician, and
- b) Telaprevir is prescribed in combination with PR (triple-drug therapy).

Note: It is recommended that patients have a baseline and TW 4 HCV RNA titer since this may be used to assess a stopping point in therapy.¹ The lag time for an HCV RNA assay may be ≤ 7 days, and may result in a lapse of therapy. Therefore, if HCV RNA titers are not available at TW 4, patients should be allowed to continue telaprevir for 12 weeks to avoid missed doses.

With telaprevir, it is recommended to assess the viral titer at TW 4 (after 4 weeks if telaprevir/PR). In patients with HCV RNA $> 1,000$ IU/mL at TW 4, it is recommended to discontinue telaprevir/PR.¹ In the ILLUMINATE (treatment-naïve supplemental study), patients with HCV RNA $> 1,000$ IU/mL were discontinued from telaprevir (but could continue to receive PR).⁸ Very few patients in ADVANCE and ILLUMINATE had HCV RNA $> 1,000$ IU/mL at TW 4 (1.7% and 1.5%, respectively), these patients discontinued telaprevir at TW 4, but were allowed to continue with PR, and none of the patients achieved SVR.¹⁵ In ILLUMINATE the proportion of patients with RVR (HCV RNA < 50 IU/mL) at TW 4 was 72%.⁸ No data are currently available to describe the proportion of retreatment patients with HCV RNA $> 1,000$ IU/mL at TW 4.¹⁵ Telaprevir is not recommended to be continued in patients with HCV RNA $> 1,000$ IU/mL at TW 4.¹

Treatment-naïve. Telaprevir is FDA-approved for treatment naïve patients with genotype 1 chronic HCV for 12 weeks in combination with PR.¹ Patients with HCV RNA $> 1,000$ IU/mL at TW 4 or TW 12 should discontinue telaprevir. The recommended duration of PR following telaprevir is based on achieving eRVR. In patients with eRVR, PR is administered for 12 weeks following telaprevir/PR (total treatment duration 24 weeks). In patients with non-eRVR (that is detectable HCV RNA $< 1,000$ IU/mL at TW 4 and/or TW 12) PR is administered alone for 36 weeks (total treatment duration 48 weeks).

Retreatment. Telaprevir is FDA-approved for retreatment in patients with genotype 1 chronic HCV who have not responded to (partial-responder or null-responder) or have relapsed after prior PR therapy.¹ Examples of medications that may have been previously used are the interferons (Intron A[®], Roferon A[®], Pegasys[®], PEGIntron[®]) with or without ribavirin. Relapse is defined as HCV RNA undetectable at the end of treatment, but detectable within 24 weeks of treatment follow-up (non-SVR). A null-responder is defined as a patient with $< 2 \log_{10}$ reduction in HCV RNA at TW 12 of a

prior course of PR. A partial-responder is defined as a patient with a $\geq 2 \log_{10}$ reduction in HCV RNA at TW 12, but not achieving undetectable HCV RNA at the end of prior PR treatment.

The recommended duration of treatment in prior null-responders and prior partial-responders is 12 weeks of telaprevir/PR followed by 36 weeks of PR for a total treatment duration of 48 weeks. The recommended dosing regimen in prior relapse patients is based on achieving eRVR. In patients with eRVR, PR is administered for 12 weeks following telaprevir/PR (total treatment duration 24 weeks). In patients with non-eRVR (that is detectable HCV RNA $< 1,000$ IU/mL at TW 4 and/or TW 12) PR is administered alone for 36 weeks (total treatment duration 48 weeks). Patients with HCV RNA $> 1,000$ IU/mL at TW 4 or TW 12 should discontinue telaprevir.

The approved labeling for telaprevir recommends RGT in prior relapsers. In the pivotal Phase III retreatment study (REALIZE), RGT was not used in relapse patients. In REALIZE, all patients received 36 weeks of PR following telaprevir/PR for a total duration of treatment of 48 weeks.⁴ In prior relapsers, SVR was achieved in 83% to 88% of patients treated with telaprevir vs. 24% for PR ($P < 0.0001$).

The pivotal trial in previously treated patients with chronic HCV mono-infection (REALIZE) included patients who had failed prior therapy for HCV with PR.⁷ The population included previous null-responders, partial-responders, and relapsers. Telaprevir was administered for 12 weeks in combination with PR, followed by 36 weeks of PR for a total treatment duration of 48 weeks.⁷ SVR was observed in significantly more non-responders treated with telaprevir compared with PR (41% vs. 9%, respectively [$P < 0.0001$]). In a secondary analysis, according to prior non-response, SVR rates (vs. PR) in partial-responders (59% vs. 15% [$P < 0.001$]), and null-responders (29% vs. 5% [$P < 0.0001$]), were significantly greater with telaprevir than PR.

Cirrhosis. Telaprevir is FDA-approved for the treatment of patients with genotype 1 chronic HCV and compensated cirrhosis.¹ The recommended duration of therapy in patients with compensated cirrhosis/fibrosis is 48 weeks (12 weeks of telaprevir PR followed by 36 weeks of PR alone).¹ Patients with HCV RNA $> 1,000$ IU/mL at TW 4 or TW 12 should discontinue telaprevir.

In ADVANCE, 21% of patients had advanced fibrosis/cirrhosis. Limited data are available in this subset; however, treatment with telaprevir improved the rate of SVR compared with PR alone. In ADVANCE the proportion of patients with SVR was 62% for telaprevir12/PR vs. 33% for PR alone. In ILLUMINATE, 16% and 11% of patients had bridging fibrosis or cirrhosis, respectively. The overall rate of SVR was 63% in patients with bridging fibrosis or cirrhosis. In patients with eRVR; 82% and 88% of patients achieved SVR in the 24-week treatment arm and the 48-week treatment arm, respectively.

Other uses with supportive evidence

2. **Adult patients with Hepatitis B virus (HBV)/chronic HCV genotype 1 co-infection.** Approve telaprevir using FDA-approved indication (above) for mono-infected patients. There are no data on the use of telaprevir in patients with HBV/HCV co-infection. In the expert opinion of a reviewer we have adopted this criterion.

EXCLUSIONS

Coverage of telaprevir is not recommended in the following circumstances:

1. **Patients with non-genotype 1 chronic HCV infection.** The safety and efficacy of telaprevir in patients with HCV and non-genotype 1 infection have not been established. Telaprevir is indicated for patients with genotype 1 chronic HCV infection.¹ A Phase IIa study (abstract) reported results of

the activity of telaprevir monotherapy or telaprevir/PR in treatment-naïve *genotype 4* HCV patients (n = 24).¹¹ SVR was reported for 62.5%, 50% and 62.5% of patients treated with telaprevir/PR, telaprevir, and PR respectively following 48 weeks of therapy. Relapse was reported in one, two, and one patient(s) treated with telaprevir/PR, telaprevir, and PR respectively following 48 weeks of therapy. A Phase 2a study assessing the viral kinetics and safety of telaprevir in treatment-naïve patients with genotype 2 or 3 chronic HCV (n = 16) has been completed; no results are available.¹² Larger studies are needed.

2. **Patients with chronic HCV and human immune deficiency (HIV) co-infection.** Although currently under investigation¹³, the safety and efficacy of telaprevir in patients with HCV/HIV co-infection have not been established.¹ Telaprevir should not be used in patients with HCV/HIV co-infection outside of carefully designed clinical trials.¹⁴ Interim results (abstract) from a Phase IIa study of telaprevir/PR in interferon-naïve patients with HIV and chronic genotype 1 HCV co-infection (n = 60) have been presented.¹³ At the time of the report 21 patients had reached Week 12. The study is ongoing for the assessment of SVR. Patients were randomized to telaprevir12/PR followed by 36 weeks of PR or placebo/PR for 48 weeks. When telaprevir was used with an efavirenz-containing ART regimen, the dose of telaprevir was increased from 750 mg three times daily (TID) to 1,125 mg TID. The proportion of patients achieving eRVR for a telaprevir-containing arm was 49% vs. 0% for PR. In patients treated with a higher dose of telaprevir (due to efavirenz containing ART) 62% of patients achieved eRVR. Fully published results are needed to determine the optimal dosing regimen and to establish safety with HIV antiretroviral medications.
3. **Patients with recurrent hepatitis C after liver (or other organ) transplantation.** There are no data available on the use of telaprevir in patients after liver or other organ transplantation.¹
4. **Monotherapy with telaprevir.** Telaprevir monotherapy is not recommended. Telaprevir monotherapy, that is, telaprevir not concomitantly prescribed with PR cannot be recommended.¹ Rapid emergence of resistance has been reported when oral protease inhibitors such as telaprevir are used without PR.³ The protease inhibitors (e.g., telaprevir) have a low genetic barrier to resistance and have been shown to select resistant HCV variants *in vitro*. There are no indications for telaprevir monotherapy. Telaprevir must be prescribed in combination with PR.¹
5. **Pediatric patients (age < 18 years).** The safety and efficacy of telaprevir have not been established in pediatric patients. Telaprevir is indicated for use in adult patients with genotype 1 chronic HCV.
6. **Patient has failed therapy with telaprevir or another NS3/4A protease inhibitor for HCV (e.g., boceprevir [Victrelis™]).** The efficacy of telaprevir in patients who have previously failed therapy with a treatment regimen containing telaprevir or other HCV NS3/4A protease inhibitor (e.g., boceprevir) has not been established.¹
7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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