



Boceprevir (Victrelis™) UTILIZATION MANAGEMENT CRITERIA

DRUG CLASS:	Protease Inhibitors
BRAND (generic) NAME:	Victrelis (boceprevir) Capsules 200 mg

FDA-APPROVED INDICATIONS

Victrelis (boceprevir) is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

The following points should be considered when initiating Victrelis for treatment of chronic hepatitis C infection:

- Victrelis must not be used as monotherapy and should only be used in combination with peginterferon alfa and ribavirin.
- Victrelis efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes Victrelis or other HCV NS3/4A protease inhibitors.
- Victrelis in combination with peginterferon alfa and ribavirin has not been studied in patients documented to be historical null responders (less than a 2-log₁₀ HCV-RNA decline by treatment week 12) during prior therapy with peginterferon alfa and ribavirin. The clinical studies included subjects who were poorly interferon responsive. Subjects with less than 0.5-log₁₀ HCV-RNA decline in viral load at Treatment Week 4 with peginterferon alfa plus ribavirin alone are predicted to have a null response (less than 2-log₁₀ viral load decline at Treatment Week 12) to peginterferon alfa and ribavirin therapy.
- Poorly interferon responsive patients who were treated with Victrelis in combination with peginterferon alfa and ribavirin have a lower likelihood of achieving a sustained virologic response (SVR), and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to peginterferon alfa and ribavirin.

COVERAGE AUTHORIZATION CRITERIA

Boceprevir (Victrelis) is covered for the following condition and situations:

Chronic Hepatitis C in treatment-naïve patients or retreatment in patients with genotype 1 chronic HCV who have not responded to (partial-responder or null-responder) or have relapsed after prior interferon-based therapy.

INITIAL THERAPY

- Patient is 18 years of age or older, AND
- Baseline positive viral load (quantitative HCV-RNA) test, AND
- Confirmed genotype 1, AND
- The patient has compensated liver disease (Child-Pugh score <6), AND
- The patient has completed, or will be completing, a 4-week “lead-in” with peginterferon alfa (i.e., Peg-Intron or Pegasys) and ribavirin prior to initiating boceprevir, AND
- Boceprevir is prescribed in combination with both peginterferon (Peg-Intron or Pegasys) and ribavirin, AND
- Boceprevir is prescribed by or in consultation with a physician with expertise and experience in the management of infectious hepatitis, AND
- The patient has not previously failed a course of therapy that included a protease inhibitor used to treat hepatitis C (e.g., boceprevir or telaprevir), AND
- No contraindicated drug interactions with boceprevir are present (e.g., coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, or potent CYP3A4/5 inducers). (See Table 2 below.), AND
- Not covered in pregnant women and men whose female partners are pregnant (ribavirin contraindication).

APPROVAL DURATION

- Approval of boceprevir for 44 weeks (maximum FDA-labeled duration for total boceprevir therapy) will be given in patients
 - with compensated cirrhosis, OR
 - with null response to prior interferon-based therapy, OR
 - naïve to hepatitis C treatment and who did not achieve a decline from baseline in HCV-RNA of 0.5- \log_{10} or more at Treatment Week 4 with peginterferon alfa plus ribavirin alone
- Approval of boceprevir for 32 weeks will be given in patients without cirrhosis who experienced partial response or relapse to prior interferon-based therapy.
- Patients without cirrhosis who are naïve to treatment
 - **INITIAL THERAPY:** Approval of boceprevir for 12 weeks
 - **RENEWAL EVALUATION:**
 - Patients whose HCV RNA at Treatment Week 8 is undetectable – Approval of boceprevir for an additional 12 weeks
 - Patients whose HCV RNA at 8 weeks is detectable – Approval of boceprevir for an additional 20 weeks

WARNINGS AND PRECAUTIONS:**Use of Victrelis with Ribavirin and Peginterferon alfa:**

- **Ribavirin may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients.** Patients must have a negative pregnancy test prior to therapy; use two or more forms of contraception, and have monthly pregnancy tests.
- **Anemia** - The addition of Victrelis to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations compared with peginterferon alfa and ribavirin alone.
- **Neutropenia** - The addition of Victrelis to peginterferon alfa and ribavirin may result in worsening of neutropenia associated with peginterferon alfa and ribavirin therapy alone.

CONTRAINDICATIONS:**All contraindications to peginterferon alfa and ribavirin also apply since Victrelis must be administered with peginterferon alfa and ribavirin.**

- Because ribavirin may cause birth defects and fetal death, boceprevir in combination with peginterferon alfa and ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant
- Coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
- Potent CYP3A4/5 inducers where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy.

DOSAGE AND ADMINISTRATION**Victrelis/Peginterferon Alfa/Ribavirin Combination Treatment**

Victrelis must be administered in combination with peginterferon alfa and ribavirin. The dose of Victrelis is 800 mg (four 200-mg capsules) three times daily (every 7-9 hours) with food [a meal or light snack] (see Table 1).

The following dosing recommendations differ for some subgroups from the dosing studied in the Phase 3 trials. Response-Guided Therapy (RGT) is recommended for most individuals, but longer dosing is recommended in targeted subgroups (e.g., patients with cirrhosis).

Victrelis Combination Therapy: Patients Without Cirrhosis Who Are Previously Untreated or Who Are Previous Partial Responders or Relapsers to Interferon and Ribavirin therapy

- Initiate therapy with peginterferon alfa and ribavirin for 4 weeks (Treatment Weeks 1-4).
- Add Victrelis 800 mg (four 200-mg capsules) orally three times daily (every 7-9 hours) to peginterferon alfa and ribavirin regimen after 4 weeks of treatment. Based on the patient's HCV-RNA levels at Treatment Week (TW) 8, TW12 and TW24, use the following Response-Guided Therapy (RGT) guidelines to determine duration of treatment (see Table 1).

Table 1: Duration of Therapy Using Response-Guided Therapy (RGT) Guidelines in Patients Without Cirrhosis Who Are Previously Untreated or Who Are Previous Partial Responders or Relapsers to Interferon and Ribavirin Therapy

	ASSESSMENT* (HCV-RNA Results**)		RECOMMENDATION
	At Treatment Week 8	At Treatment Week 24	
Previously Untreated Patients	Undetectable	Undetectable	Complete three-medicine regimen at TW28.
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48.
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete three-medicine regimen at TW36.
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48.
<p>*TREATMENT FUTILITY If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.</p> <p>**In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL.</p>			

Response-Guided Therapy was not studied in subjects who had less than a 2-log₁₀ HCV-RNA decline by treatment week 12 during prior therapy with peginterferon alfa and ribavirin. If considered for treatment, these subjects should receive 4 weeks of peginterferon alfa and ribavirin followed by 44 weeks of Victrelis 800 mg orally three times daily (every 7-9 hours) in combination with peginterferon alfa and ribavirin. In addition, consideration should be given to treating previously untreated patients who are poorly interferon responsive (as determined at TW4) with 4 weeks peginterferon alfa and ribavirin followed by 44 weeks of Victrelis 800 mg orally three times daily (every 7-9 hours) in combination with peginterferon alfa and ribavirin in order to maximize rates of SVR.

Victrelis Combination Therapy: Patients with Cirrhosis

Patients with compensated cirrhosis should receive 4 weeks peginterferon alfa and ribavirin followed by 44 weeks Victrelis 800 mg (four 200-mg capsules) three times daily (every 7-9 hours) in combination with peginterferon alfa and ribavirin.

Dose Modification

- Dose reduction of Victrelis is not recommended.
- If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dose should be reduced or discontinued. Refer to the peginterferon alfa and ribavirin Package Inserts for additional information

about how to reduce and/or discontinue the peginterferon alfa and/or ribavirin dose. Victrelis must not be administered in the absence of peginterferon alfa and ribavirin.

Discontinuation of Dosing Based on Treatment Futility

Discontinuation of therapy is recommended in all patients with 1) HCV-RNA levels of greater than or equal to 100 IU/mL at TW12; or 2) confirmed detectable HCV-RNA levels at TW24.

REFERENCES:

Victrelis (boceprevir) product labeling. Schering Corporation, a subsidiary of Merck & Co. Whitehouse Station, NJ. 2011. http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf

Table 2

Drugs that are contraindicated with Victrelis

(Drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events, and potent CYP3A4/5 inducers where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy)

Drug Class	Drugs Within Class that are Contraindicated With Victrelis	Clinical Comments
Alpha 1-Adrenoreceptor antagonist	Alfuzosin	Increased alfuzosin concentrations can result in hypotension
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response to Victrelis
Antimycobacterial	Rifampin	May lead to loss of virologic response to Victrelis.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's Wort (<i>hypericum perforatum</i>)	May lead to loss of virologic response to Victrelis.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis
Oral Contraceptives	Drospirenone	Potential for hyperkalemia
PDE5 enzyme Inhibitor	REVATIO [®] (sildenafil) or ADCIRCA [®] (tadalafil) when used for the treatment of pulmonary arterial hypertension*	Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/Hypnotics	Triazolam; orally administered Midazolam*	Prolonged or increased sedation or respiratory depression.

*See Victrelis product labeling for information on the coadministration of sildenafil and tadalafil when dosed for erectile dysfunction, and for information on parenterally administered midazolam.