Therapeutic Class Overview
Hepatitis C Protease Inhibitors

Therapeutic Class

- **Overview/Summary:** Included in this review are the hepatitis C protease inhibitors boceprevir (Victrelis®) and telaprevir (Incivek®). Both agents are Food and Drug Administration (FDA) approved for the treatment of adults with chronic hepatitis C genotype 1 infection, when used in combination with pegylated interferon alfa and ribavirin. The hepatitis C protease inhibitors can be used in both treatment naïve and experienced patients, and the specific FDA approved indications are outlined in Table 1.[1,2] These new direct acting antivirals inhibit the replication of hepatitis C virus (HCV) host cells by binding to the NS3/4A protease of HCV genotype 1a and 1b.[1-3] Because these agents must be used in combination with pegylated interferon alfa and ribavirin, the contraindications and warnings associated with those agents are also applicable to the hepatitis C protease inhibitors. In addition, the incidences of anemia and rash are increased when the hepatitis C protease inhibitors are used in combination with pegylated interferon alfa and ribavirin. Both boceprevir (2,400 mg/day) and telaprevir (2,250 mg/day) are administered three times daily.[1,2] The most efficacious therapy for the treatment of hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with pegylated interferon alfa and ribavirin.[4,5] No one pegylated interferon or ribavirin product is preferred or recommended over another.[4-9] Clinical trials have demonstrated that when a hepatitis C protease inhibitor its added to the current standard of care sustained virologic response rates are significantly increased.[10-14] Furthermore, no one hepatitis C protease inhibitor is preferred over another and current recommendations for their use are in line with FDA approved indications and dosing.[4,5]

Table 1. Current Medications Available in Therapeutic Class[1,2]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Boceprevir (Victrelis®)	Treatment of chronic hepatitis genotype 1 infection, in combination with pegylated interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy	Capsule: 200 mg	-
Telaprevir (Incivek®)	Treatment of chronic hepatitis genotype 1 infection, in combination with pegylated interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers	Tablet: 375 mg	-

Evidence-based Medicine

Clinical trials evaluating the safety and efficacy of the hepatitis C protease inhibitors demonstrated that when used in combination with standard therapy (i.e., pegylated interferon alfa and ribavirin) significantly higher sustained virologic response rates were achieved compared to standard therapy alone in adults with chronic hepatitis C genotype 1 infection. These results were achieved in both treatment naïve and experienced patients. Additionally, results demonstrated that in select patients who achieve an early virologic response with a hepatitis C protease inhibitor-containing regimen, there is potential to decrease the total duration of treatment (24 [telaprevir], 28 [boceprevir] or 36 [boceprevir] vs 48 weeks [standard therapy]). Use of a hepatitis C protease inhibitor was also associated with a greater incidence of adverse events, including anemia and rash, compared to the standard therapy alone.[10-14]

Key Points within the Medication Class

- According to Current Clinical Guidelines:

- The most efficacious therapy for the treatment of hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with pegylated interferon alfa and ribavirin.[4,5]
  - No one pegylated interferon or ribavirin product is preferred or recommended over another.[4-9]
  - Patients with genotype 2 or 3 infection may receive treatment for up to 24 weeks and patients with genotype 1 or 4 infection may receive treatment for up to 48 weeks.
- Patients with hepatitis C genotype 1 infection may be treated with a nonstructural protein 3 protease inhibitor, along with standard of care.[4,5]
  - No one protease inhibitor is preferred or recommended over another.

· Other Key Facts:

- Boceprevir is available as a 200 mg capsule and is dosed 800 mg three times daily.[1]
  - Boceprevir is initiated after a four week lead-in period of pegylated interferon alfa and ribavirin alone.
- Telaprevir is available as a 375 mg tablet and is dosed 750 mg three times daily.[2]
  - Telaprevir is initiated with pegylated interferon alfa and ribavirin.
- When added to standard therapy, both boceprevir and telaprevir are associated with an increase in the incidence of anemia. In addition, telaprevir is associated with an increase incidence in rash, which can be serious in nature.[1,2]
- Select patients with a satisfactory early virologic response to a hepatitis C protease inhibitor-containing regimen are appropriate for shorter duration of total treatment.[1,2]
  - If a patient has an undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) level at treatment weeks eight and 24 with a boceprevir-containing regimen, 28 or 36 weeks of total treatment is effective in achieving a sustained virologic response (SVR).
  - If a patient has an undetectable HCV RNA level at treatment weeks four and 12 with a telaprevir-containing regimen, 24 weeks of total treatment is effective in achieving an SVR.
- Futility rules, based on HCV RNA levels, apply to any triple therapy regimen used for the treatment of chronic hepatitis C genotype 1 infection.[1,2]
  - Futility should be assessed at treatment weeks 12 and 24 with boceprevir-containing regimens, and at treatment weeks four, 12 and 24 with telaprevir-containing regimens

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Therapeutic Class Review
Hepatitis C Protease Inhibitors

Overview/Summary

The hepatitis C virus (HCV) is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood. It causes chronic infection in 70 to 85% of infected persons and the Centers for Disease Control and Prevention estimates 3.2 million persons are chronically infected. Chronic HCV infection can lead to the development of active liver disease, and accounts for up to 40% of all patients undergoing liver transplantation.[1,2] There are six genotypes of HCV (genotypes 1 to 6), with genotype 1 being the most common within the United States, followed by genotypes 2 and 3. Genotyping is helpful in the clinical management of patients with hepatitis C for predicting the likelihood of response to treatment and in determining the optimal duration of treatment.[3] Treatment goals for the management of chronic hepatitis C include preventing complications and death. Due to the slow evolution of chronic infection it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Of most importance is sustained virologic response (SVR), which is defined as the absence of HCV ribonucleic acid 24 weeks following discontinuation of treatment.[3] Of note, SVR rates are lowest with genotype 1 as compared to the other identified genotypes.[4] Combination treatment with pegylated interferon and ribavirin remains the standard of care for the treatment of chronic hepatitis C.[3-7] Newer treatment strategies which aim to improve efficacy, ease of administration, tolerability and patient adherence, as well as shorten treatment duration are currently being developed and include the newly approved nonstructural protein 3 protease inhibitors.[4] According to the American Association for the Study of Liver Diseases, the new protease inhibitors are recommended, along with standard of care, in patients with genotype 1 chronic hepatitis C.[5] Overall, guidelines do not give preference to one specific pegylated interferon or ribavirin product over another.[3-7] Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with Food and Drug Administration (FDA)-approved indications and dosing.[4,5]

Included in this review are the hepatitis C protease inhibitors boceprevir (Victrelis®) and telaprevir (Incivek®). Both agents are FDA-approved for the treatment of adults with chronic hepatitis C genotype 1 infection, when used in combination with pegylated interferon alfa and ribavirin. Both agents can be used in treatment naïve and experienced patients, and the specific FDA-approved indications are outlined in Table 2.[8,9] These new direct acting antivirals inhibit the replication of HCV host cells by binding to the NS3/4A protease of HCV genotype 1a and 1b.[8-10] In general, clinical trials demonstrate that use of these protease inhibitors, in combination with standard of care, yields higher SVR rates, with a potential to decrease the total duration of treatment (24 [telaprevir], 28 [boceprevir] or 36 [boceprevir] compared to 48 weeks [standard of care]) in patients who achieve an early virologic response. In clinical trials, use of boceprevir or telaprevir was associated with a greater incidence of anemia and rash compared to standard of care.[2,3,11-15]

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Boceprevir (Victrelis®)	Hepatitis C protease inhibitor	-
Telaprevir (Incivek®)	Hepatitis C protease inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications[8,9]

Indication	Boceprevir	Telaprevir
Treatment of chronic hepatitis genotype 1 infection, in combination with pegylated interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy	a	
Treatment of chronic hepatitis genotype 1 infection, in combination with		a

Indication	Boceprevir	Telaprevir
pegylated interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers		

There are additional factors that should be considered before initiating therapy with either boceprevir or telaprevir. These agents should never be used as monotherapy and should only be used in combination with pegylated interferon alfa and ribavirin. The efficacies of boceprevir or telaprevir have not been evaluated in patients who have previously failed therapy with a treatment regimen that includes either agent or other hepatitis C virus (HCV) nonstructural protein 3/4A protease inhibitors.[8,9]

With regard to boceprevir-containing regimens, efficacy has not been evaluated in patients documented to be historical null responders (<2 $\log_{10}$ HCV ribonucleic acid decrease by treatment week 12) during prior therapy with pegylated interferon alfa and ribavirin. Clinical trials included patients who were classified as poor responders to interferon (patients who had a nonresponse or relapse). Poorly interferon responsive patients treated with a boceprevir-containing regimen 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 pegylated interferon alfa and ribavirin.[8]

With regard to telaprevir-containing regimens, a high proportion of previous null responders, particularly those with cirrhosis, did not achieve a SVR and had telaprevir resistance-associated substitutions emerge on treatment with telaprevir-containing regimens.[9]

Pharmacokinetics

Table 3. Pharmacokinetics[10]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Boceprevir	Not reported	9	None	3.4
Telaprevir	Not reported	1	R diastereomer*	9 to 11

*30-fold less active compared to telaprevir.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the hepatitis C protease inhibitors are outlined in Table 4. Data from clinical trials support the Food and Drug Administration (FDA)-approved indications and dosing recommendations for these agents. Overall, the addition of hepatitis C protease inhibitors to standard therapy (i.e., pegylated interferon alfa and ribavirin) is associated with a significant increase in sustained virologic response (SVR) (undetectable hepatitis C virus [HCV] ribonucleic acid [RNA] levels 24 weeks after completion of treatment) rates. The addition of these agents to standard therapy is also associated with a higher incidence of adverse events, including anemia and rash.[11-19]

Based on the FDA-approved dosing for boceprevir, patients are required to initiate standard therapy for a period of four weeks before initiating treatment with boceprevir.[8] This is based on phase II trial data in which it was determined that in order to decrease the rate of viral breakthrough and relapse in patients receiving boceprevir, HCV RNA levels should be lowered as much as possible before initiation of boceprevir.[18]
Poordad et al evaluated the safety and efficacy of boceprevir, in combination with standard therapy, in treatment naïve adults with chronic HCV genotype 1 infection (SPRINT-2; N=1,097). Patients were excluded if they were co-infected with human immunodeficiency virus (HIV) or hepatitis B. There were three treatment regimens (control [i.e., standard therapy], response guided therapy and fixed duration therapy), which all included a four week lead-in period in which only standard therapy was administered. Of note, self-described nonblack and black patients were enrolled into two separate cohorts due to the marked difference in rates of SVR between these two populations (nonblack; N=938, black; N=159). The control regimen consisted of an additional 44 weeks of standard therapy (48 weeks of treatment total). Response guided therapy consisted of 24 weeks of boceprevir plus standard therapy, at which point if a rapid virologic response (undetectable HCV

RNA at treatment week eight through 24) was achieved, treatment was considered complete (28 weeks of treatment total). However, if a rapid virologic response was not achieved, standard therapy alone was continued for an additional 20 weeks (48 weeks of treatment total). Fixed duration therapy consisted of 44 weeks of boceprevir plus standard therapy (48 weeks of treatment total). All patients were followed for a total of 72 weeks, which included either 24, 44 or 48 weeks of follow up, depending on total treatment duration.[11]

For SPRINT-2, the primary efficacy endpoint of SVR was significantly higher with response guided and fixed duration therapies (i.e., boceprevir-containing regimens) among the nonblack and black cohorts, compared to control. Specifically, within the nonblack cohort, SVR rates were 40 (N=311), 67 (N=316) and 68% (n =311) with control, response guided therapy and fixed duration therapy (*P*<0.001 vs control for both). Within the black cohort, the corresponding rates were 23 (N=52), 42 (N=52) and 53% (N=55) (*P*=0.04 vs control for response guided therapy and *P*=0.004 vs control for fixed duration therapy).[11]

Subgroup analyses of SPRINT-2 revealed that regardless of the degree of HCV RNA decrease from baseline after a four week lead-in period with standard therapy (<1 or ≥1 $\log_{10}$ IU/mL), the addition of boceprevir was consistently more likely to result in SVR compared to standard therapy alone. Overall, however, a decrease of <1 $\log_{10}$ IU/mL (poor interferon response) was associated with lower SVR rates and higher rates of boceprevir-resistance-associated variants. In addition, the SVR rates among patients with undetectable HCV RNA levels at treatment week eight were high regardless of treatment regimen; however, patients receiving boceprevir-containing regimens were three times more likely to achieve this early virologic response compared to patients receiving standard therapy alone. With regard to response guided and fixed duration therapies, SVR rates within the nonblack cohort were similar (67 vs 68%; *P* value not reported), whereas within the black cohort they were higher with fixed duration therapy (42 vs 53%; *P* value not reported). Furthermore, among nonblack patients treated with a boceprevir-containing regimen who had an early virologic response (HCV RNA level undetectable at treatment week eight) (60%), and those who remained undetectable through 24 weeks of treatment (47%), the SVR rate was similar between response guided (24 weeks of boceprevir) and fixed duration (44 weeks of boceprevir) therapies (97 vs 96%; *P* value not reported). Similar SVR rates between response guided and fixed duration therapies were also observed among patients who did not have an early response (74% for each). Fatigue, headache and nausea were the most common adverse events reported in all treatment groups, with dysgeusia and anemia occurring more frequently with boceprevir-containing regimens.[11]

Results from SPRINT-2 demonstrated that the addition of boceprevir to standard therapy significantly increased the SVR rate among treatment naïve adult patients with chronic HCV genotype 1 infection, with an increased incidence of anemia. The data also supports the efficacy of response guided therapy, which consisted of individualized treatment duration based on HCV RNA levels between treatment weeks eight and 24.

Bacon et al evaluated the safety and efficacy of boceprevir, in combination with standard therapy, in treatment experienced adult patients with chronic HCV genotype 1 infection (RESPOND-2, N=403). In this trial, patients had to have demonstrated previous responsiveness to interferon based therapy (minimum of 12 weeks), but experienced either a nonresponse (decrease in the HCV RNA level ≥2 $\log_{10}$ IU/mL by treatment week 12 of prior therapy, but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR) or relapse (undetectable HCV RNA level at the end of prior therapy without subsequent attainment of a SVR). RESPOND-2 and SPRINT-2 were similar in design in that patients co-infected with HIV or hepatitis B were excluded, there were three treatment regimens (control [N=80], response guided therapy [N=162] and fixed duration therapy [N=161]) and all treatment regimens consisted of a four week lead-in period with standard therapy alone. In contrast, RESPOND-2 did not separate nonblack and black patients and, as mentioned previously, patients were treatment experienced. Similar to SPRINT-2, the control regimen consisted of standard therapy for an additional 44 weeks (48 weeks of total treatment) and the fixed duration therapy consisted of boceprevir plus standard therapy for 44 weeks (48 weeks of total treatment). Response guided therapy consisted of boceprevir plus standard therapy for 32 weeks, if at which point HCV RNA levels were undetectable at treatment weeks eight and 12, treatment was considered complete (36 weeks of total treatment). However, if the HCV RNA level was detectable at treatment week eight and undetectable at treatment week 12, standard therapy alone was continued for an additional12 weeks (48 weeks of total

treatment). All patients were followed for a total of 72 weeks which included either 24, 36 or 60 weeks of follow up, depending on treatment duration.[15]

For RESPOND-2, the primary efficacy endpoint of SVR was again significantly higher with response guided and fixed duration therapies (i.e., boceprevir-containing regimens) compared to control. Specifically, SVR rates were 21, 59 and 66% with control, response guided therapy and fixed duration therapy, respectively (*P*<0.001 vs control for both). Among the two subgroups of treatment experienced patients, those with a prior relapse (29, 69 and 75% with control, response guided and fixed duration therapies, respectively) or prior nonresponse (7 vs 40 and 52%, respectively) both had higher SVR rates with boceprevir-containing regimens compared to standard therapy alone. With regards to response guided and fixed dose therapies, no difference was observed in overall SVR rates (odds ratio, 1.4; 95% confidence interval [CI], 0.9 to 2.2). In addition, of the patients who responded poorly to therapy (HCV RNA level decrease <1 $\log_{10}$ IU/mL at treatment week four), SVR was more likely to be achieved with boceprevir-containing regimens compared to standard therapy alone (0 vs 33 and 34%, respectively; *P* values not reported) and similar results were observed among good responders (HCV RNA level decrease ≥1 $\log_{10}$ IU/mL) (25 vs 73 and 79%, respectively; *P* values not reported). The proportions of patients who achieved an early response (undetectable HCV RNA level at treatment week eight), were 46 and 52% with response guided and fixed duration therapies, respectively, which was approximately six times higher compared to control (9%). Serious adverse events and anemia were reported more frequently with boceprevir-containing regimens.[15]

Results from RESPOND-2 demonstrated that the addition of boceprevir to standard therapy significantly increased the SVR rate among treatment experienced adult patients with chronic HCV genotype 1 infection. The data also suggested that boceprevir-containing regimens may be more effective in achieving SVR in patients with a previous relapse (69 to 75%) compared to those who experienced a nonresponse to previous therapy (40 to 52%). Similar to SPRINT-2, achievement of an early virologic response resulted in similar SVR rates with response guided therapy (32 weeks of boceprevir) and fixed duration therapy (44 weeks of boceprevir), further supporting the notion that patients who respond early to treatment with a boceprevir-containing regimen may be appropriate for a shorter duration of total treatment.

Based on the FDA-approved dosing of telaprevir, patients can initiate triple therapy (i.e., telaprevir plus standard therapy) at the same time. In contrast to boceprevir, there is no lead-in period with standard therapy alone required before initiation of telaprevir.[9]

Jacobson et al evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment naïve adult patients with chronic HCV genotype 1 infection (ADVANCE; N=1,088). Patients were excluded if they had decompensated liver disease, liver disease from other causes or hepatocellular carcinoma. There were three treatment regimens (control [N=361] and two response guided therapies [N=727]). The control regimen consisted of 48 weeks of standard therapy (48 weeks of total treatment). The two response guided therapies were T12/PR (N=363) and T8/PR (N=364). T12/PR consisted of telaprevir plus standard therapy for 12 weeks, and depending on whether or not an extended rapid virologic response (undetectable HCV RNA at treatment week four that remained undetectable at week 12) was achieved or not, standard therapy was continued for an additional 12 (24 weeks of treatment total) or 36 weeks (48 weeks of total treatment). T8/PR consisted of telaprevir plus standard therapy for eight weeks, followed by standard therapy alone for an additional four weeks. At which point, depending on whether or not an extended rapid virologic response was achieved, standard therapy alone was administered for an additional 12 (24 weeks of treatment total) or 36 weeks (48 weeks of treatment total). All patients were followed for a total of 72 weeks.[12] For ADVANCE, the primary efficacy endpoint of SVR was significantly higher with both response guided therapies (75 [*P*<0.0001 vs control], 69 [*P*<0.0001 vs control] and 44% with T12/PR, T8PR and control, respectively), with no difference observed between T12/PR and T8/PR (treatment difference, 6%; 95% CI, -12.5 to 0.6). When the results were analyzed according to extended rapid virologic response, fibrosis stage or race, SVR rates were consistently higher with telaprevir-containing regimens; however, comparisons were not always significant compared to control. Data suggests that 12 weeks of telaprevir may be more effective than eight weeks. Specifically, 12 weeks of telaprevir resulted not only in a nonsignificantly higher SVR rate, but also in a lower virologic failure rate (8 vs 13%; *P* value not reported). The difference in the rate of virologic failure was noted to be due to a higher failure rate in patients after telaprevir was discontinued. Beyond week

12, the rates of virologic failure were higher with T8PR compared to T12PR (10 vs 5%, respectively), with more frequent emergence of wild-type and lower-level resistant variants. Adverse events were reported more frequently with telaprevir-containing regimens included pruritis, nausea, rash, anemia and diarrhea.[12,19]

Results from ADVANCE demonstrated that the addition of telaprevir to standard therapy significantly increased the SVR rate among treatment naïve adult patients with chronic HCV genotype 1 infection, with an increased incidence of both rash and anemia. The data also demonstrated that 12 weeks of telaprevir is more efficacious than eight weeks.

Sherman et al also evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment naïve adult patients with chronic HCV genotype 1 infection (ILLUMINATE; N=540). In contrast to the other clinical trials, ILLUMINATE was an open-label, noninferiority trial. In this trial, patients were excluded if they were co-infected with HIV or hepatitis B. All patients received telaprevir plus standard therapy for 12 weeks, followed by standard therapy alone for an additional eight weeks. If at treatment week 20, an extended rapid virologic response was not achieved; standard therapy alone was administered for an additional 28 weeks (48 weeks of total treatment). If at treatment week 20 an extended rapid virologic response was achieved; standard therapy was administered for either an additional four (T12/PR24, 24 weeks of total treatment) or 28 weeks (T12PR48, 48 weeks of total treatment). Patients were followed for a total of 72 weeks.[13]

For ILLUMINATE, the primary efficacy endpoint of SVR with T12PR24 compared to T12PR48 was similar (92 vs 88%; 95% CI, -2 to 11; *P* value not reported). Overall, 332 patients achieved an extended rapid virologic response, and 162 and 160 were randomly assigned to T12PR24 and T12PR48. The SVR rate among patients who did not achieve an extended rapid virologic response (N=118) was 64%.[13,19]

Results from ILLUNIMATE support the concept that select patients who achieve an early virologic response with telaprevir-containing regimens may be appropriate for a shorter duration of total treatment.

Zeuman et al evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment experienced adult patients with chronic HCV genotype 1 infection (REALIZE; N=662). Patients in this trial consisted of prior relapsers (undetectable HCV RNA level at the end of prior therapy without subsequent attainment of a SVR), partial responders (decrease in HCV RNA level ≥2 $\log_{10}$ IU/mL by treatment week 12 of prior therapy, but not achieving HCV RNA undetectable status at the end of prior therapy) and null responders (decrease in HCV RNA level <2 $\log_{10}$ IU/mL at treatment week 12 of prior therapy). There were three treatment regimens evaluated in the REALIZE trial (control, lead-in therapy and nonlead-in therapy). The control regimen consisted of standard therapy for 48 weeks (48 weeks of total treatment). The lead-in regimen (Lead-in T12PR48) consisted of standard therapy for four weeks, followed by telaprevir plus standard therapy for an additional 12 weeks, followed by standard therapy alone for an additional 32 weeks (48 weeks total of treatment). The non-lead-in regimen (T12PR48) consisted of telaprevir plus combination with standard therapy for 12 weeks, followed by standard therapy alone for an additional 36 weeks (48 weeks of total treatment). All patients were followed for a total of 72 weeks.[16]

For REALIZE, the primary efficacy endpoint of SVR was significantly higher with both telaprevir-containing regimens (66 [*P*<0.001 vs control], 64 [*P*<0.001 vs control] and 17% with Lead-in T12PR48, T12PR48 and control), with no difference observed between Lead-in T12PR48 and T12PR48 (*P* value not reported). Among the various subpopulations of treatment experienced patients, SVR rates were consistently significantly higher with telaprevir-containing regimens (*P*<0.0001 for all comparisons). Subgroup analyses according to the stage of liver fibrosis or baseline viral load resulted in higher SVR rates with telaprevir-containing regimens compared to control. Reported adverse events were consistent with those described in other clinical trials evaluating telaprevir.[16,19]

Results from REALIZE demonstrated that the addition of telaprevir to standard therapy significantly increased the SVR rate among treatment experienced adult patients with chronic HCV genotype 1 infection. The data also supports the FDA-approved dosing of telaprevir in that no lead-in period is required and patients can initiate triple therapy at the same time.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hepatitis C				
Poordad et al[11] SPRINT-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response guided therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 24 weeks, followed by an additional 20 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at any visit from week 8 to 24 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. The trial consisted of two cohorts enrolling nonblacks and blacks separately.	PC, PG, RCT Patients ≥18 years of age with a history of no previous treatment for HCV infection, weight 40 to 125 kg, chronic infection with HCV genotype 1 and plasma HCV RNA level ≥10,000 IU/mL	N=1,097 (N=938 [nonblack], N=159 [black]) 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Not reported	Primary: Among nonblack patients, the rate of SVR was 40, 67 and 68% in Groups 1, 2 and 3 (*P*<0.001 vs Group 1 for both Group 2 and 3). The corresponding numbers in black patients were 23, 42 (*P*=0.04 vs Group 1) and 53% (*P*=0.004 vs Group 1). Subgroup analyses revealed that at four weeks, 23 and 38% of nonblack and black patients had a decrease of <1 $\log_{10}$ IU/mL in HCV RNA level from baseline, which was associated with lower rates of SVR and higher rates of boceprevir-resistance-associated variants compared to those achieving a decrease of ≥1 $\log_{10}$ IU/mL from baseline. However, regardless of the degree of reduction achieved at week four, patients receiving boceprevir achieved consistently higher rates of SVR compared to patients who received control overall. Adverse events occurred in more than 98% of all patients, with serious adverse events in 9, 11 and 12% of patients in Groups 1, 2 and 3, respectively. There were six deaths during the trial; four deaths in Group 1 and two deaths from boceprevir-containing regimens. Two suicides (one in Group 1 and one in Group 2) were determined to have possibly been related to treatment with peginterferon. Fatigue, headache and nausea were the most commonly reported adverse events. The incidence of dysgeusia was higher with boceprevir treatment. Anemia was reported in 29 and 49% of patients receiving control and boceprevir, respectively. Overall, 13 and 21% of control- and boceprevir-treated patients required dose reductions because of anemia and erythropoietin was administered in 24 and 43% of patients. Neutropenia and thrombocytopenia also occurred more frequently with boceprevir treatment. Secondary: Not reported Response rates at the end of therapy (undetectable HCV RNA level at the time that the study therapy was discontinued) were significantly higher with boceprevir-containing regimens compared to the control regimen.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment was considered complete in Group 2 if the HCV RNA level was undetectable from week 8 through week 24 (total duration, 28 weeks). In all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 24 based on futility rules; these patients then entered the follow up period.				Among nonblack patients, viral breakthrough (undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) occurred in one to two percent of all patients, regardless of treatment regimen. In addition, relapse rates (undetectable HCV RNA level at the end of treatment but a detectable HCV RNA level at some point during the follow up period) were lower with boceprevir compared to control. The numbers of events among black patients were too few to permit comparison between the treatment groups.
Jacobson et al[12] ADVANCE Telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 12 weeks, followed by an additional 12 or 36 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T12PR) vs telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 8 weeks, followed by an additional 16 or 40 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T8PR) vs	DB, PC, PG, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection with no previous treatment	N=1,088 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of patients with undetectable HCV RNA at week 72, four, 12 or both four and 12, at the end of treatment and 12 weeks after the last planned dose of treatment; safety	Primary: SVR rates were significantly higher with telaprevir-containing regimens compared to control (75, 69 and 44% with T12PR, T8PR and control (*P*<0.001 for T12PR and T8PR vs control). Secondary: Seventy three, 67 and 44% of patients receiving T12PR, T8PR and control had undetectable HCV RNA 72 weeks after starting treatment (*P*<0.001 for T12PR and T8PR vs control). Sixty eight, 66 and nine percent of patients, respectively, had undetectable HCV RNA at week four (rapid virologic response), and 58, 57 and eight percent of patients, respectively, had undetectable HCV RNA at weeks four and 12 (extended rapid virologic response) (*P* values not reported). Among patients with an extended rapid virologic response assigned to receive a total of 24 weeks of therapy, SVR rates were 89 and 83% with T12PR and T8PR (*P* value not reported). Among patients who had undetectable HCV RNA levels after the last dose of treatment, relapse rates were nine, nine and 28% with T12PR, T8PR and control (*P* values not reported). Subgroup analyses demonstrated that SVR rates were higher with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 48 weeks (control) Patients in the T12PR and T8PR groups who met criteria for an extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12) received 12 additional weeks of treatment with peginterferon alfa-2a plus ribavirin (24 total weeks of treatment). Patients who had detectable HCV RNA either at week 4 or 12 received an additional 36 weeks of peginterferon alfa-2a plus ribavirin (48 total week of treatment).				telaprevir-containing regimens. Subgroup analyses included HCV genotype subtype (1a and 1b), African Americans, baseline HCV RNA levels (≥800,000 IU) and bridging fibrosis or cirrhosis. The incidence of gastrointestinal disorders, pruritis, rash and anemia was ≥10 percentage points higher with telaprevir-containing regimens. A total of 10, 10 and seven percent of patients receiving T12PR, T8PR and control discontinued all treatment at some time during the trial owing to adverse events (*P* values not reported); with seven, eight and four percent of these patients discontinuing during the telaprevir (or placebo) phase. Anemia and rash were the most frequently reported adverse events that lead to discontinuation. One case of Stevens-Johnson syndrome occurred approximately 11 weeks after the last dose of telaprevir had been administered.
Sherman et al[13] ILLUMINATE Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day plus telaprevir 750 mg three times a day for 12 weeks (T12PR12), followed by peginterferon alfa-2a plus ribavirin for 12 or 36 weeks. Patients who achieved an extended rapid virologic response (undetectable HCV RNA levels at weeks 4 and 12) after 20 weeks were randomized to continue peginterferon alfa-2a plus ribavirin for an additional 4 (24 weeks total	MC, NI, OL, RCT Patients 18 to 70 years of age with chronic hepatitis C genotype 1 infection for ≥6 months, no previous treatment and with no hepatitis B or HIV	N=540 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR in T12PR24 compared to T12PR48 Secondary: Not reported	Primary: The absolute difference in SVR rate between T12PR24 vs T12PR48 was four percentage points (92 vs 88%; 95% CI, -2 to 11). The lower limit of this 95% CI (-2%) exclude the NI margin -10.5%. The SVR rate in patients who did not achieve an extended rapid virologic response therefore received a total of 48 weeks of treatment was 64% (76/118) Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatment; T12PR24) or 28 weeks (48 total weeks of treatment; T12PR48). Patients who did not achieve an extended rapid virologic response after 20 weeks received peginterferon alfa-2a plus ribavirin for an additional 28 weeks (48 total weeks of treatment).				
Kumada et al[14] (Group A) Telaprevir 750 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 12 weeks, followed by an additional 12 weeks of peginterferon alfa-2a plus ribavirin vs (Group B) Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 48 weeks	AC, DB, MC, RCT Patients 20 to 65 years of age with chronic HCV genotype 1 infection who had not received prior treatment and had a current HCV RNA ≥5.0 $\log_{10}$ IU/mL, no hematologic abnormalities and a weight of 40 to 120 kg	N=189 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR, nonresponder rate, proportion of patients with an RVR at week four, safety and adverse events Secondary: Not reported	Primary: Treatment with telaprevir (Group A) was associated with a statistically significant increase in SVR rate (73.0 vs 49.2%; *P*=0.0020) compared to standard of care (Group B). The nonresponder rate was significantly lower in Group A (triple therapy) compared to Group B (0.8 vs 20.6%; *P*<0.0001). A higher proportion of women achieved an SVR in Group A compared to Group B (70.0 vs 43.3%; *P*=0.0214). In addition, patients ≥50 years of age achieved a significantly higher SVR in Group A compared to Group B (67.1 vs 42.9%; *P*=0.0125). Furthermore, more patients with a high HCV RNA viral load at baseline (≥7 $\log_{10}$ IU/ml) achieved a SVR in Group A compared to Group (69.2 vs 27.8%; *P*=0.0132). A significantly greater proportion of patients achieved a RVR at four weeks in Group A compared to Group B (84.0 vs 4.8%; *P*<0.0001). The most commonly reported adverse events were anemia, pyrexia, leukocytopenia, thrombocytopenia and malaise. Drugs were discontinued due to adverse events in a similar number of patients in Groups A and B (16.7 vs 22.2%, respectively; *P* value not reported). Telaprevir was discontinued in 19.0% of patients in Group A. Anemia occurred in 91.3 and 73.0% of patients in Groups A and B, respectively. Combined, Grade 1 and 2 anemia was more common in Group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A compared to Group B (38.1 vs 17.5%; *P*=0.0045). Grade 3 anemia occurred in 11.1% in Group A only. During the follow-up, hemoglobin increased both in Groups A and B, and returned to pretreatment levels 12 weeks after the completion of therapy. Skin disorders occurred in a similar proportion of patients in Groups A and B (89.7 vs 84.1%, respectively; *P* value not reported). Most skin disorders were mild and categorized as Grade 1. Combined, skin disorders of Grades 2 to 4 occurred more frequently in Group A than Group B (46.8 vs 23.8%; *P*=0.0026). Serious skin disorders developed in three patients in Group A, but zero patients in Group B. Stevens-Johnson syndrome occurred in one patient after 35 days of treatment and led to the discontinuation of treatment.
Hepatitis C - Retreatment				
Bacon et al[15] RESPOND-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response guided therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 32 weeks, followed by an additional 12 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at week 8 but undetectable at week 12 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day	PC, PG, RCT Patients with chronic HCV genotype 1 infection who demonstrated responsiveness to interferon (minimum duration of therapy, 12 weeks)	N=403 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Proportion of patients with an early response in whom a SVR was achieved, proportion of patients with a relapse	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to control, with overall rates of SVR of 21, 59 and 66% in Groups 1, 2 and 3, respectively (*P*<0.001). The increase observed with Groups 2 and 3 was largely due to end of treatment rates of response being higher (70 and 77 vs 31%) and relapse rates being lower (15 and 12 vs 32%) compared to Group 1. The absolute difference between Groups 2 and 1 was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups 3 and 1 it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups 2 and 3 (OR, 1.4; 95% CI, 0.9 to 2.2). Overall, the most common adverse events were flulike symptoms, while dysgeusia, rash and dry skin were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events, and there were more discontinuations and dose modifications due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (43 to 46 vs 20%), and erythropoietin was administered more frequently to patients receiving boceprevir. Secondary: The proportion of patients with an undetectable HCV RNA level at week eight in Groups 2 and 3 (46 and 52%) was approximately six times the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable at weeks 8 and 12 (total duration, 36 weeks). In addition, in all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				proportion in Group 1 (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86 and 88% in Groups 1, 2 and 3; *P* values not reported). The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 29, 69 and 75% in Groups 1, 2 and 3; respectively (*P* values not reported). And the patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), the corresponding rates were 7, 40 and 52% (*P* values not reported). Virologic breakthrough (achievement of an undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) and incomplete virologic response (an increase of 1 $\log_{10}$ IU/mL in the HCV RNA level from the nadir, with an HCV RNA level >1,000 IU/mL) were infrequent during the treatment period. Multivariable stepwise logistic-regression analysis served to identify five baseline factor that were significantly associated with achievement of a SVR: assignment to boceprevir (OR for Groups 2 and 3 vs Group 1, 7.3 and 10.7, respectively; *P*<0.001 for both), previous relapse (OR vs previous nonresponse, 3.1; *P*<0.001), low viral load at baseline (OR vs high load, 2.5; *P*=0.02) and absence of cirrhosis (OR vs presence, 2.1; *P*=0.04).
Zeuman et al[16] REALIZE Telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an additional 36 weeks of peginterferon alfa-2a plus ribavirin (T12PR48) vs	DB, PC, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no SVR to 1 previous course of peginterferon alfa and ribavirin	N=662 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Effect of lead-in treatment with peginterferon alfa-2a plus ribavirin on SVR,	Primary: Compared to control, SVR rates were significantly higher with telaprevir-containing regimens in patients who had a previous relapse (83, 88 and 24% with T12PR48, Lead-in T12PR48 and control), for those who did not have a previous virologic response (41, 41 and 9%), including those who had a partial response (59, 54 and 15%) and those who had no response (29, 33 and 5%) (*P*<0.001 for all comparisons). SVR rates were similar with T12PR48 and Lead-in T12PR48 among patients who had a relapse or no response or a partial response to previous therapy (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 4 weeks, followed by telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an additional 32 weeks of peginterferon alfa-2a plus ribavirin (Lead-in T12PR48) vs peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 48 weeks (control) Patients could have 1 of 3 previous responses to peginterferon alfa plus ribavirin therapy; no response (reduction <2 log_{10} in HCV RNA after 12 weeks of therapy), partial response (reduction ≥2 log_{10} in HCV RNA after 12 weeks of therapy but with detectable HCV RNA) or relapse (undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter).	despite receiving at least 80% of the intended dose		proportion of patients who had undetectable HCV RNA at four and eight weeks, relapse, change from baseline in log_{10} HCV RNA, safety	Secondary: Overall, SVR rates were 64, 66 and 17% with T12PR48, Lead-in T12PR48 and control. Differences was 47 percentage points between T12PR48 and control (95% CI, 37 to 57; *P*<0.001) and 50 percentage points between Lead-in T12PR48 and control (95% CI, 40 to 60; *P*<0.001). In patients with a previous relapse, the proportion of patients with an undetectable HCV RNA were 70 and 93, three and 89 and three and 10% with T12PR48, Lead-in T12PR48 and control (*P* values not reported). In patients with a previous partial response, the corresponding proportions were 65 and 82, zero and 65 and zero and zero percent (*P* values not reported). Relapse rates were lower with telaprevir-containing regimens among patients who had a previous relapse or no response or a partial response to previous therapy. Changes in log_{10} HCV RNA levels are provided in graphic form only. The most frequently reported adverse events (>25% of patients) with telaprevir were fatigue, pruritus, rash, nausea, influenza-like illness, anemia and diarrhea. Serious adverse events (12 vs 5%) and those leading to treatment discontinuation (13 vs 3%) were more frequent with telaprevir.
Hayashi et al[17] Telaprevir 750 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for	MC, OL Patients 20 to 65 years of age with chronic HCV genotype 1	N=141 (109 relapsers and 32 non-responders)	Primary; SVR, relapse, breakthrough, nonresponse and safety	Primary: The SVR rate was 88.1% (96/109) in patients who were prior relapsers to treatment and 34.4% in patients who were previous nonresponders to treatment 34.4% (11/32). The RVR and ETR rates in prior relapsers were 87.2% (95/109) and 94.5%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
12 weeks, followed by an additional 12 weeks of peginterferon alfa-2a plus ribavirin	infection who were relapsers or nonresponders to a previous course of peginterferon alfa and ribavirin with a current HCV RNA ≥5.0 log_{10} IU/mL, no hematologic abnormalities and a weight of 40 to 120 kg	24 weeks (plus 24 weeks of follow up)	Secondary: Not reported	(103/109), respectively (P values not reported). In prior nonresponders, the RVR and ETR rates were 71.9% (23/32) and 59.4% (19/32), respectively. In prior relapsers, the SVR rate in the patients who achieved undetectable HCV RNA at week four was significantly higher compared to patients achieving undetectable HCV RNA after week four of treatment (91.8 vs 66.7%; *P*=0.0487). In the prior nonresponder group, undetectable HCV RNA at week four did not appear to have an effect on SVR rates (39.1 vs 28.6%; *P*=1.0). The SVR rate in previous relapsers was significantly higher in males compared to females (93.9 vs 79.1%; *P*=0.0316), while there was no difference in SVR rate between genders in patients who were previous nonresponders to therapy. The rates of nonresponse, breakthrough and relapse were 0.9% (1/109), 0.9% (1/109) and 7.3% (8/109), respectively, in patients who were prior relapsers. The incidence of nonresponse, breakthrough and relapse in prior nonresponders was 6.3% (2/32), 18.8% (6/32) and 40.6% (13/32), respectively. The incidence of adverse events was similar between the prior relapsers and prior nonresponders. Serious adverse events were reported in 11.9% (13/109) of prior relapsers and 9.4% (3/32) of prior nonresponders. Overall, the most frequently reported adverse events in prior relapsers and prior nonresponders were anemia (88.1 vs 100%, respectively), pyrexia (82.6 vs 93.8%, respectively), decreased white blood cell count (76.1 vs 69.8%, respectively), blood uric acid increase (66.1 vs 78.1%, respectively) and platelet count decrease (67.0 vs 68.6%, respectively). Overall, 17.4% of prior relapsers discontinued treatment due to adverse events compared to 12.5% of prior nonresponders. Anemia was the most frequently reported adverse event leading to discontinuation in both treatment groups. Adverse events related to skin disorders were observed in 82.3% (116/141)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				of patients. Skin disorders reported in over 10% of the patients were rash 39.0% (55/141), drug eruption in 24.1% (34/141), injection site reaction in 12.8% (18/141) and injection site erythema in 12.8% (18/141) of the patients. Despite ribavirin dose modification, the median hemoglobin levels in prior relapsers and prior nonresponders decreased to 10.6 and 10.4 g/dL at week 12, respectively. No patient discontinued all the study drugs because of a neutrophil decrease. Secondary: Not reported

Study abbreviations: CI=confidence interval, DB=double blind, MC=multicenter, NI=non-inferiority, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: ETR=end of treatment response, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IU=international units, RNA=ribonucleic acid, RVR=rapid viral response, SVR=sustained virologic response

Special Populations

Table 5. Special Populations[8,9]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Boceprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	B*	Unknown; use with caution.
Telaprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild impairment; use is not recommended in moderate to severe impairment.	B*	Unknown; use with caution.

*Ribavirin has a pregnancy category of X.

Adverse Drug Events

The adverse events reported in clinical trials for boceprevir (regardless of causality) with a frequency ≥10% of patients receiving boceprevir in combination with pegylated interferon and ribavirin, and reported at a rate ≥5% than pegylated interferon and ribavirin alone are outlined in Table 6. In addition, adverse events reported in clinical trials with a frequency ≥5% higher among patients receiving telaprevir in combination with pegylated interferon and ribavirin compared to pegylated interferon and ribavirin alone are also outlined in Table 6.[8,9]

Table 6. Adverse Drug Events (%)[8,9]

Adverse Event(s)	Boceprevir*	Telaprevir
Blood and Lymphatic System Disorders		
Anemia	50/45	36
Neutropenia	25/14	-
Central Nervous System		
Dizziness	19/16	-
Insomnia	34/30	-
Irritability	22/21	-
Gastrointestinal		
Anal pruritis	-	6
Anorectal discomfort	-	11
Diarrhea	25/24	26
Dry mouth	11/15	-
Dysgeusia	35/44	10
Hemorrhoids	-	12
Nausea	46/43	39
Vomiting	20/15	13
General Disorders and Administration Site Conditions		
Asthenia	15/21	-
Chills	34/33	-
Fatigue	58/55	56
Metabolism and Nutrition Disorders		
Decreased appetite	25/26	-
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	19/23	-

Adverse Event(s)	Boceprevir*	Telaprevir
Respiratory		
Dyspnea, exceptional	8/11	-
Skin and Subcutaneous Tissue Disorders		
Alopecia	27/22	-
Dry skin	18/22	-
Pruritis	-	47
Rash	17/16	56

- Event not reported or incidence <1%.
*Reported as: treatment naïve patients/previous treatment failures (percent/percent).

Contraindications/Precautions

The hepatitis C protease inhibitors are contraindicated in women who are or who may become pregnant and in men whose female partners are pregnant because of the risk for birth defects and fetal death associated with ribavirin. In addition, these agents are contraindicated when combined with drugs that are highly dependent on cytochrome P450 (CYP) 3A4 clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These agents are also contraindicated when combined with drugs that strongly induce CYP3A, which may lead to a lower exposure and reduced efficacy of hepatitis C protease inhibitors. Medications that are contraindicated with either boceprevir or telaprevir include: alfuzosin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort, lovastatin, simvastatin, pimozide, sildenafil, tadalafil, triazolam, or orally-administered midazolam. In addition, carbamazepine, phenobarbital, phenytoin, and drospirenone are contraindicated with the use of boceprevir, while atorvastatin is contraindicated with the use of telaprevir. [8,9]

Because the hepatitis C protease inhibitors must be used in combination with pegylated interferon alfa and ribavirin, the contraindications and warnings associated with those agents are also applicable to the hepatitis C protease inhibitors (Black Box Warnings associated with these agents are outlined below). Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Women of childbearing potential and men must use at least two forms of effective contraception during treatment, and for at least six months after treatment has ended. Systemic hormonal contraceptives may not be as effective in women taking hepatitis C protease inhibitors; therefore, two alternative effective methods of contraception (e.g., intrauterine devices, barrier methods) should be used in women during treatment with these agents.[8,9]

Anemia has been reported in patients receiving pegylated interferon alfa and ribavirin, and the addition of a hepatitis C protease inhibitor is associated with an additional decrease in hemoglobin concentrations. Complete blood counts should be monitored prior to and at least every four weeks during treatment with a hepatitis C protease inhibitor. For the management of anemia, ribavirin dose reductions should be used. If ribavirin dose reductions are inadequate, consideration to discontinuing treatment with a hepatitis C protease inhibitor should be evaluated along with the ribavirin therapy.[8,9]

Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome were reported in less than one percent of patients receiving telaprevir in combination with pegylated interferon alfa and ribavirin compared to those who received only pegylated interferon alfa and ribavirin. Presenting signs of DRESS may include rash, fever, facial edema and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. Presenting symptoms of SJS may include fever, target lesions and mucosal erosions or ulcerations (e.g., conjunctivae, lips). If serious skin reactions develop in patients receiving telaprevir, all treatment must be discontinued immediately. In addition, rash developed in 56% of patients who received telaprevir in combination with pegylated interferon alfa and ribavirin. Patients with mild to moderate rashes should be followed, and if the rash progresses and becomes severe or if systemic symptoms develop, telaprevir must be discontinued; however, pegylated interferon alfa and ribavirin may be continued.[8,9]

As mentioned previously, according to the Food and Drug Administration approved package labeling of the hepatitis C protease inhibitors, these agents are not to be used as monotherapy and must be administered with pegylated interferon alfa and ribavirin.

Black Box Warning for Pegasys® (peginterferon alfa-2a) and PegIntron® (peginterferon alfa-2b)[20,21]

WARNING
Alfa interferons, including peginterferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a or alfa-2b therapy. Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

Black Box Warnings for Copegus® (ribavirin), Rebetol® (ribavirin) and Ribasphere®/Ribasphere® RibaPak® (ribavirin)[22-24]

WARNING
Ribavirin monotherapy is no effective for the treatment of chronic hepatitis C virus infection and should not be used along for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Drug Interactions

Table 7. Drug Interactions[25]

Generic Name	Interacting Medication or Disease	Potential Result
Hepatitis C protease inhibitors (all)	α-1 adrenergic blockers	α-1 adrenergic blocker plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Hepatitis C protease inhibitors (all)	Barbiturates	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Barbiturate concentrations may be elevated or reduced.
Hepatitis C protease inhibitors (all)	Benzodiazepines	Plasma concentrations of certain benzodiazepines may be elevated, increasing the pharmacologic effects and risk of severe sedation and prolonged respiratory depression.
Hepatitis C protease inhibitors (all)	Carbamazepine	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Carbamazepine concentrations may be elevated, increasing the risk of adverse reactions.
Hepatitis C protease inhibitors (all)	Cisapride	Cisapride plasma concentrations may be elevated, increasing the pharmacologic effects and risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Hepatitis C protease inhibitors (all)	Contraceptives, hormonal	Plasma concentrations of certain progestins may be elevated, increasing the risk of hyperkalemia. Estrogen concentrations may be reduced, increasing the risk of unintended pregnancy.
Hepatitis C	Ergot derivatives	Ergot derivative plasma concentrations may be elevated,

Generic Name	Interacting Medication or Disease	Potential Result
protease inhibitors (all)		increasing the pharmacologic effects and risk of adverse reactions.
Hepatitis C protease inhibitors (all)	Hydantoins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Hydantoin concentrations may be elevated or reduced.
Hepatitis C protease inhibitors (all)	Rifamycins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Rifamycin concentrations may be elevated, increasing the risk of adverse reactions.
Hepatitis C protease inhibitors (all)	St. John's Wort	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response
Hepatitis C protease inhibitors (all)	Tacrolimus	Tacrolimus plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including QT prolongation.

Dosage and Administration

Both boceprevir and telaprevir are administered three times daily with food, and both agents are to be administered in combination with pegylated interferon alfa and ribavirin. In addition, both agents have specific guidelines as to response guided therapy which are based on hepatitis C virus (HCV) ribonucleic acid (RNA) levels at certain treatment weeks. General dosing recommendations for boceprevir and telaprevir are outlined in Table 8, while the recommendations for response guided therapy are outlined in Tables 9 & 10.[8,9]

Boceprevir is added to pegylated interferon alfa and ribavirin after a four week lead-in period of pegylated interferon alfa and ribavirin alone, and is administered for either 24 or 32 weeks depending on the patient's treatment history and HCV RNA levels.[8] Telaprevir can be initiated with pegylated interferon alfa and ribavirin and is administered for 12 weeks regardless of treatment history or HCV RNA levels. In general, patients with inadequate viral response are unlikely to achieve sustained virologic response, and may develop treatment-emergent resistance substitutions.[9]

Table 8. Dosing and Administration[8,9]

Generic Name	Adult Dose	Pediatric Dose	Availability
Boceprevir	Treatment of chronic hepatitis genotype 1 infection, in combination with pegylated interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy: Capsule: initial, after four weeks of pegylated interferon alfa and ribavirin administer 800 mg TID (every seven to nine hours) with food	Safety and efficacy in children have not been established.	Capsule: 200 mg
Telaprevir	Treatment of chronic hepatitis genotype 1 infection, in combination with pegylated interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers: Tablet: 750 mg TID (every seven to nine hours) with food for 12 weeks	Safety and efficacy in children have not been established.	Tablet: 375 mg

TID=three times daily

Table 9. Boceprevir Response Guided Treatment in Patients Without Cirrhosis[8]

	Assessment* (HCV RNA Results†)		Recommendation‡
	At Treatment Week Eight	At Treatment Week 24	
Treatment Naïve Patients	Undetectable	Undetectable	Complete boceprevir, pegylated interferon alfa and ribavirin at treatment week 28
	Detectable	Undetectable	Continue boceprevir, pegylated interferon alfa and ribavirin and finish through treatment week 36; then administer pegylated interferon alfa and ribavirin and finish at treatment week 48
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete boceprevir, pegylated interferon alfa and ribavirin at treatment week 36
	Detectable	Undetectable	Continue boceprevir, pegylated interferon alfa and ribavirin and finish through treatment week 36; then administer pegylated interferon alfa and ribavirin and finish at treatment week 48

HCV=hepatitis C virus, RNA=ribonucleic acid
*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥100 IU/mL at treatment week 12, discontinue boceprevir, pegylated interferon alfa & ribavirin. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue boceprevir, pegylated interferon alfa & ribavirin.
†In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TagMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 9.3 IU/mL.
‡Includes the four week lead in phase of pegylated interferon and ribavirin therapy.

Patients with cirrhosis should receive four weeks of pegylated interferon alfa and ribavirin followed by 44 weeks of boceprevir 800 mg three times daily in combination with pegylated interferon alfa and ribavirin.[8]

Table 10. Telaprevir Response Guided Treatment[9]

	Assessment* (HCV RNA Results†)	Recommendations		
		Triple Therapy (Telaprevir, Pegylated Interferon alfa and Ribavirin)	Dual Therapy (Pegylated Interferon alfa and Ribavirin)	Total Treatment Duration
Treatment Naïve and Prior Relapse Patients	Undetectable at treatment weeks four and 12	First 12 weeks	Additional 12 weeks	24 weeks
	Detectable (≤1,000 IU/mL) at treatment weeks four and/or 12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients	All patients	First 12 weeks	Additional 36 weeks	48 weeks

HCV=hepatitis C virus, IU=international units, RNA=ribonucleic acid
*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥1,000 IU/mL at treatment week four or 12, discontinue telaprevir, pegylated interferon alfa and ribavirin. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue pegylated interferon alfa and ribavirin.
†In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TagMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 9.3 IU/mL.

Treatment naïve patients with cirrhosis who have an undetectable hepatitis C virus ribonucleic acid level at treatment weeks four and 12 may benefit from an additional 36 weeks of pegylated interferon alfa and ribavirin.[9]

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases: **An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011)**[5]	· The optimal therapy for hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with pegylated interferon alfa and ribavirin. · Boceprevir and telaprevir should not be used without pegylated interferon alfa and weight based ribavirin. Treatment naïve patients · The recommended dose of boceprevir is 800 mg three times daily (every seven to nine hours) with food plus pegylated interferon alfa and weight based ribavirin for 24 to 44 weeks, preceded by four weeks of lead in pegylated interferon alfa plus ribavirin alone. o Patients without cirrhosis treated with boceprevir, pegylated interferon alfa and ribavirin, whose HCV ribonucleic acid (RNA) levels at weeks eight and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (four weeks lead in of combination therapy only, followed by 24 weeks of triple therapy). o Triple therapy should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. · The recommended dose of telaprevir is 750 mg three times daily (every seven to nine hours) with food (not low fat) plus pegylated interferon alfa and weight based ribavirin for 12 weeks followed by an additional 12 to 36 weeks of pegylated interferon alfa plus ribavirin alone. o Patients without cirrhosis treated with telaprevir, pegylated interferon alfa and ribavirin, whose HCV RNA level at weeks four and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks. o Triple therapy should be stopped if the HCV RNA levels is >1,000 IU/mL at treatment weeks four or 12 and/or detectable at treatment week 24. · Patients with cirrhosis treated with either boceprevir or telaprevir in combination with pegylated interferon alfa and ribavirin should receive therapy for a duration of 48 weeks. Treatment experienced patients · Retreatment with boceprevir or telaprevir, in combination with pegylated interferon alfa and weight based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or pegylated interferon alfa and/or ribavirin. · Retreatment with telaprevir, in combination with pegylated interferon alfa and weight based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or pegylated interferon alfa and/or weight based ribavirin. · Response guided therapy of treatment experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders but cannot be recommended for null responders. · Patients re-treated with boceprevir plus pegylated interferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance.

Clinical Guideline	Recommendation(s)
	· Patients re-treated with telaprevir plus pegylated interferon alfa and ribavirin who continue to have detectable HCV RNA >1,000 IU at weeks four or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. Adverse events · Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. · Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (greater than one log increase in serum HCV RNA above nadir) is observed. · Patients who fail to have a virological response, who experience virological breakthrough or who relapse on one protease inhibitor should not be retreated with other protease inhibitors. IL28B testing · IL28B genotype is a robust pretreatment predictor of sustained virologic response (SVR) to pegylated interferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with chronic HCV genotype 1. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment needed.
Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office: **Update on the management and treatment of hepatitis C virus infection (2012)**[26]	Recommendations in patients being considered for HCV therapy: · All patients with chronic hepatitis C virus (HCV) infection should be evaluated for HCV antiviral treatment. · Patients should be counseled on their likelihood of achieving sustained virologic response (SVR), based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy. · IL28B genotype testing can be performed before pegylated interferon-ribavirin therapy with or without a protease inhibitor, if the results would alter treatment decisions. Recommendations for treatment-naïve patients with genotype 1 infection: · Pegylated interferon alfa and ribavirin, in combination with boceprevir (800 mg three times daily with food) or telaprevir (750 mg three times daily with 20 grams of fat), is the standard of care for most treatment-naïve genotype 1-infected patients. · If a telaprevir-containing regimen is used in treatment-naïve noncirrhotic patients who achieve an extended rapid virologic response (eRVR), telaprevir should be discontinued at week 12 and pegylated interferon-ribavirin should be continued for an additional 12 weeks. If HCV ribonucleic acid (RNA) is detectable at week four, but <1,000 IU/ml and remains <1,000 IU/mL or becomes undetectable at week 12, telaprevir should be discontinued at week 12, and pegylated interferon-ribavirin can be continued for another 36 weeks. · If a telaprevir-containing regimen is used in treatment-naïve cirrhotics who achieve an HCV RNA that is undetectable or <1,000 IU/mL at treatment weeks four and 12, telaprevir should be discontinued at week 12, and pegylated interferon-ribavirin can be continued for 36 more weeks. · If a boceprevir-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥1 $\log_{10}$ during the four-week lead-in, and HCV RNA is undetectable at weeks eight to 24, treatment with boceprevir-pegylated interferon-ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at

Clinical Guideline	Recommendation(s)
	week eight, but <100 IU/mL at week 12 and negative at week 24, boceprevir-pegylated interferon-ribavirin should be continued until week 36, followed by pegylated interferon-ribavirin alone for 12 more weeks. If HCV RNA declines by <1 $\log_{10}$ during the lead-in, boceprevir-pegylated interferon-ribavirin can be continued for 44 weeks. · If a boceprevir-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of boceprevir-pegylated interferon-ribavirin is required after the four-week lead-in. <u>Recommendations for treatment of nonresponders and relapsers with genotype 1 infection:</u> · For patients who previously failed pegylated interferon-ribavirin, retreatment with boceprevir or ribavirin and pegylated interferon-ribavirin may be considered, particularly in patients who were relapsers. · If a boceprevir-containing regimen is used for retreatment of noncirrhotic prior partial responders or relapsers, the treatment duration should be 36 weeks if HCV RNA is undetectable from weeks eight to 24. If HCV RNA is detectable at week 12, but <100 IU / mL and is undetectable from weeks 24 to 36, boceprevir can be discontinued at week 36 and pegylated interferon-ribavirin can be continued for an additional 12 weeks. · If a boceprevir-containing regimen is used for retreatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. · If a boceprevir-containing regimen is used for retreatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. · If a telaprevir-containing regimen is used for retreatment of prior relapsers, and HCV RNA is undetectable from weeks four and 12, telaprevir should be discontinued at week 12 and pegylated interferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable, but <1000 IU/mL at week four and/or 12, telaprevir can be discontinued at week 12, and pegylated interferon-ribavirin can be continued for an additional 36 weeks. · If a telaprevir-containing regimen is used for retreatment of prior partial responders or null responders, and HCV RNA is <1000 IU/mL at weeks four and 12, telaprevir should be discontinued at week 12 and pegylated interferon-ribavirin should be continued for an additional 36 weeks. <u>Recommendations for dose modification:</u> · Pegylated interferon alfa and ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets. · If ribavirin is stopped for seven or more days in patients concomitantly receiving boceprevir or telaprevir, then also permanently discontinue the protease inhibitor. The protease inhibitors should be either continued at full dose or discontinued. · A ribavirin dose reduction should be used as initial management of HCV treatment-related anemia in a symptomatic patient with a hemoglobin <10 g/dL. Erythropoietin may be administered in patients with symptomatic anemia related to pegylated interferon-ribavirin therapy with or without protease inhibitors to limit anemia-related ribavirin dose reductions or dose discontinuations. · A pegylated interferon dose reduction should be used as initial management of HCV treatment-related neutropenia for an absolute neutrophil count of <750, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent pegylated interferon alfa dose

Clinical Guideline	Recommendation(s)
	reductions. Recommendations for treatment monitoring: · Monitor for treatment-related adverse effects at least every two weeks early in the course of therapy, and every one to two months during treatment as clinically indicated. · Treatment adherence should be assessed at every visit as well as symptoms of depression, suicidal ideation, alcohol, and illicit drug use. · Counsel patients about avoiding pregnancy through the use of two forms of contraception during treatment and for six months posttreatment. If a patient is receiving a boceprevir- or telaprevir-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners, during and for at least six months after treatment. · In patients receiving telaprevir-pegylated interferon-ribavirin, all treatment should be stopped if any of the following occur: o HCV RNA level >1,000 IU/mL at week four or 12 o Detectable HCV RNA levels at week 24 or at any timepoint thereafter o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA). · In patients receiving boceprevir-pegylated interferon-ribavirin, all treatment should be stopped if any of the following occur: o HCV RNA level ≥100 IU/mL at week 12 with a boceprevir-containing regimen o Detectable HCV RNA levels at week 24 or at any time point thereafter o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA). · Do not switch to the other protease inhibitor is virologic failure occurs with one protease inhibitor. Recommendations for groups with special considerations for therapy: · Pegylated interferon alfa monotherapy may be used to treat patients with contraindications to ribavirin. · For patients who achieve RVR and have a low baseline viral load (HCV RNA <400,000 IU/mL), 24-weeks of treatment with pegylated interferon-ribavirin may be sufficient. · Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy. · HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class <7), adequate neutrophils (>1.5 k/mm^3), and adequate platelet counts (>75 k/mm^3) should be considered for treatment with boceprevir (for 44 weeks) or telaprevir (for 12 weeks) combined with pegylated interferon-ribavirin at standard doses for 48 weeks. · Patients with cirrhosis continue to be at risk for hepatocellular carcinoma and should undergo routine screening regardless of viral clearance status. Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection: · Treatment-naïve patients should be treated with pegylated interferon-ribavirin for 24 weeks. · For patients with low viral load (HCV RNA <600,000 IU/mL) and mild fibrosis who achieve a RVR, 12 to 18 weeks of treatment may be sufficient. · For patients with genotype 3 infection and a high HCV RNA (>600,000 IU/mL), steatosis or advanced fibrosis, treatment beyond 24 weeks may

Clinical Guideline	Recommendation(s)
	improve response. · Retreatment duration is 48 weeks. Recommendations in patients with genotype 4 infection: · Appropriate candidates with HCV genotype 4 infections should be treated with pegylated interferon alfa-2a 180 µg per week or pegylated interferon alfa-2b 1.5 µg / kg per week, plus ribavirin up to 1,400 mg per day for 48 weeks. Recommendations in patients with decompensated cirrhosis: · Liver transplantation is the treatment of choice in patients with decompensated cirrhosis. · Antiviral therapy is contraindicated in most patients with decompensated cirrhosis. · Interferon-based therapy in combination with ribavirin can be considered for patients awaiting liver transplantation if they have a Child-Pugh score <7 and a Model for End-Stage Liver Disease score ≤18. · If beginning antiviral therapy, the interferon dose should be reduced and growth factors may be used to for treatment-associated cytopenias. Recommendations in patients following solid organ transplantation: · Interferon-based antiviral therapy is contraindicated in patients who have received a heart, lung or kidney transplant. · In patients with biopsy-proven chronic HCV disease following liver transplantation, pegylated interferon-ribavirin for 48 weeks may be considered. · Monitor antiviral therapy in post-liver transplant patients on antiviral therapy and discontinue if rejection is documented. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided. Recommendations in patients with renal disease: · Considered modified doses of antiviral therapy with interferon (standard or pegylated). · Antiviral therapy for HCV treatment is not recommended in patients following renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis. Recommendations in patients with comorbid conditions: · Antiviral therapy is not recommended in patients with a limited life expectancy. In addition, pegylated interferon-ribavirin, treatment should be avoided in comorbid conditions that may be exacerbated by treatment. Recommendations for patients on methadone: · Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy. Coordinated HCV treatment between providers and substance abuse specialists should occur. Recommendations in patients with ongoing alcohol use: · Encourage patients to decrease alcohol consumption or to abstain, and refer for behavioral intervention to reduce alcohol use. Antiviral therapy may be used in patients who are otherwise appropriate candidates, regardless of prior alcohol use. Alcohol reduces adherence and treatment response. Recommendations in obese patients and those with hepatic steatosis:

Clinical Guideline	Recommendation(s)
	· Patients with a body mass index >30 should be considered for antiviral treatment. Control comorbid conditions prior to initiation of antiviral therapy. Recommendations in patients with HIV/HCV coinfection: · Patients with controlled human immunodeficiency virus (HIV) infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy. Treatment should consist of pegylated interferon-ribavirin at doses similar to those with HCV for a duration of 48 weeks. Recommendations in patients with acute HCV infection: · Observe patients for eight to 20 weeks from time of initial exposure to monitor for spontaneous resolution of infection. · In patients who fail to resolve infection spontaneously, treatment with pegylated interferon alfa, with or without ribavirin for 24 to 48 weeks should be used, based on genotype and HCV RNA response during therapy.
American Association for the Study of Liver Diseases: **Diagnosis, Management, and Treatment of Hepatitis C: An Update (2009)**[3]	· Treatment decisions should be individualized based on severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions and the patient's readiness for treatment. · Optimal therapy for chronic HCV infection is pegylated interferon alfa in combination with ribavirin. · In genotypes 1 and 4, treatment with pegylated interferon alfa and ribavirin for 48 weeks is recommended. In patients who do not achieve an early virological response (early virologic response; ≥2 log reduction in HCV RNA at 12 weeks), treatment may be discontinued. Patients who do not achieve a complete early virologic response (undetectable HCV RNA at 12 weeks) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued. Finally, for patients who have delayed virus clearance (HCV RNA test becomes negative between 12 and 24 weeks); consideration should be given to extending therapy to 72 weeks. · In genotypes 2 or 3, treatment with pegylated interferon alfa and ribavirin for 24 weeks is recommended. Patients who receive treatment for 24 weeks and who have a negative HCV RNA measurement, should be retested for HCV RNA 24 weeks later to evaluate for a SVR. Regardless of genotype, patients with HCV-related cirrhosis who achieve a SVR should be monitored at six to 12 month intervals for hepatocellular carcinoma development. · The same criteria for evaluating which patients should receive treatment can be used to determine which children, age two to 17 years of age, who are infected with HCV should receive treatment. · Children should be treated with the combination of pegylated interferon alfa 2b, 60 µg/m^2 weekly, and ribavirin 15 mg/kg daily for 48 weeks.
European Association for the Study of the Liver: **Management of Hepatitis C Virus Infection (2011)**[4]	Goals and endpoints of HCV therapy · The goal of therapy is to eradicate HCV infection. · The endpoint of therapy is SVR, and once obtained, SVR usually equates to cure of infection in more than 99% of patients. · Intermediate endpoints to assess the likelihood of an SVR are HCV RNA levels at four, 12 and 24 weeks of therapy. Treatment-naïve patients · SVR is achieved in 40 to 54% of patients infected with HCV genotype 1 treated with pegylated interferon alfa plus ribavirin at approved doses for 48 weeks. · SVR is achieved in 65 to 82% of patients infected with HCV genotypes 2 or 3 treated with pegylated interferon alfa plus ribavirin at approved doses for 24

Clinical Guideline	Recommendation(s)
	weeks. · SVR rates are slightly higher in patients infected with HCV genotype 2 than those with genotype 3. · Strongest baseline predictors of SVR are: o HCV genotype. o Genetic polymorphisms located in chromosome 19 (IL28B), particularly in genotype 1 patients. o Stage of liver fibrosis. Relapsers · Patients relapsing after treatment with standard therapy regimens respond to retreatment with pegylated interferon alfa and ribavirin in 32 to 53% of cases. Nonresponders · In the most recent trials, retreatment of patients infected with HCV genotype 1 who failed previous standard therapy ranged from 4 to 14%. Contraindications to therapy · Patients with absolute contraindications to standard of care should not receive therapy. Indications for treatment · All treatment naïve patients with compensated disease due to HCV should be considered for therapy. · Treatment should be initiated promptly in patients with advanced fibrosis (METAVIR score F3 to F4), and strongly considered in patients with moderate fibrosis (F2). · In patients with less severe disease, indication for therapy is individual. First line treatment of chronic hepatitis C · The combination of pegylated interferon alfa plus ribavirin is the approved standard of care for chronic hepatitis. Two pegylated interferon alfa molecules, pegylated interferon-2α (180 µg once weekly) and pegylated interferon-α2b (1.5 µg/kg once weekly), can be used in combination with ribavirin. · Ribavirin should be administered as a weight based dose of 15 mg/kg/day for genotypes 1, 4, 5 and 6, and at a flat dose of 800 mg/day for genotypes 2 and 3. · Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at a dose of 15 mg/kg/day. Treatment monitoring · Patients treated with pegylated interferon alfa and ribavirin should be seen at a minimum of weeks four and 12 after initiation of treatment, then at a minimum of every 12 weeks until the end of treatment for both efficacy and side effects, and 24 weeks after the end of therapy to assess the SVR. · A real time polymerase chain reaction-based assay, with a lower limit of detection of 10 to 20 IU/mL is the best tool for monitoring therapy. · A low vs high baseline HCV RNA level is useful to guide treatment decisions. The best discriminating HCV RNA level is comprised between 400,000 and 800,000 IU/mL. · During treatment, HCV RNA measurements should be performed at weeks four, 12 and 24 to help tailor treatment.

Clinical Guideline	Recommendation(s)
	· The end of treatment virological response and the SVR 24 weeks after the end of treatment must be assessed. · Treatment toxicities should be assessed at weeks two and four of therapy and at four through eight week intervals thereafter. Treatment dose reductions and stopping rules · The pegylated interferon alfa dose should be reduced if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3. Pegylated interferon alfa should be stopped if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25,000/mm^3 or if severe unmanageable depression develops. · If neutrophil or platelet counts go up, treatment can be restarted, but at a reduced pegylated interferon alfa dose. · If hemoglobin <10 g/dL occurs, the dose of ribavirin should be adjusted downward by 200 mg at a time, and ribavirin should be stopped if hemoglobin falls below 8.5 g/dL. · Treatment should be stopped in case of a severe hepatitis flare or severe sepsis. Virological response guided therapy · Treatment duration should be tailored to the treatment virological response at weeks four and 12, and eventually week 24. The likelihood of SVR is directly proportional to the time of HCV RNA disappearance. · Treatment for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is <2 $\log_{10}$ IU/mL and at week 24 if HCV RNA is still detectable (≥50 IU/mL). · In patients with a rapid virologic response and low baseline viral load (<400,000 to 800,000 IU/mL), treatment for 24 weeks (genotypes 1 and 4) or 12 to 16 weeks (genotypes 2 and 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic stenosis) are present, evidence for equal efficacy of shortened treatment is insufficient. · Patients who have an early virologic response (HCV RNA which is detectable at week four but undetectable at week 12) should be treated for 48 weeks regardless of the HCV genotype and baseline viral load. · Patients with genotype 1 and a delayed virologic response can be treated for 72 weeks. This may also apply to other genotypes. Measures to improve treatment success rates · Full adherence to both pegylated interferon alfa and ribavirin should be the aim in order to optimize SVR rates. · Body weight adversely influences the response to pegylated interferon alfa and ribavirin; therefore, a reduction of body weight in overweight patients prior to therapy may increase the likelihood of SVR. · Insulin resistance is associated with treatment failure; however, insulin sensitizers have no proven efficacy in improving SVR rates in these patients. · Counseling on abstaining from alcohol during antiviral therapy should be provided. · Recombinant erythropoietin can be administered when the hemoglobin level falls <10 g/dL in order to avoid ribavirin dose reduction or discontinuation. · There is no evidence that neutropenia is associated with more frequent infection episodes, or that the use of granulocyte colony stimulating factor reduces the rate of infections and/or improves SVR rates. · Patients with a history and/or signs of depression should be seen by a

Clinical Guideline	Recommendation(s)
	psychiatrist before therapy. Patients who develop depression during therapy should be treated with antidepressants. Preventative antidepressant therapy in selected patients may reduce the incidence of this condition during treatment, without any impact on SVR. Post treatment follow up of patients who achieve an SVR · Noncirrhotic patients with SVR should be retested for alanine transaminase and HCV RNA at 48 and 96 weeks post treatment, and then discharged if alanine transaminase is normal and HCV RNA negative. · In addition to the above, cirrhotic patients with SVR should undergo surveillance for esophageal varices every one to two years and hepatocellular carcinoma every six months by means of ultrasonography and α-fetoprotein. Retreatment of nonsustained virological responders to pegylated interferon alfa and ribavirin · Patients infected with HCV genotype 1 who failed to eradicate HCV in prior therapy with pegylated interferon alfa and ribavirin should generally not be retreated with the same drug regimen. They may be considered for retreatment with the triple combination of pegylated interferon alfa, ribavirin and a protease inhibitor when available. · Nonsustained virological responders to a prior course of pegylated interferon alfa and ribavirin can be retreated with pegylated interferon alfa and ribavirin if they have urgent indication for therapy, and/or if there is evidence of inadequate exposure to either pegylated interferon alfa or ribavirin due to dose adjustments or poor compliance during the first course of treatment. · Patients infected with HCV genotypes other than 1 who failed on prior therapy with pegylated interferon alfa with or without ribavirin can be retreated with pegylated interferon alfa and ribavirin as no other options will be available soon. · Maintenance therapy with a low dose of pegylated interferon alfa is not recommended. Treatment of patients with severe liver disease · Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short to midterm complications. · Assiduous monitoring and management of side effects, especially those linked to portal hypertension and hypersplenism, is required. Growth factors are particularly useful in this group. · Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. · In patients awaiting liver transplantation, antiviral therapy, when feasible, prevents graft reinfection if an SVR is achieved. · Antiviral therapy may be started at the time of enlistment or while awaiting liver transplantation, with the goal of achieving an SVR or HCV RNA clearance before transplantation. · Antiviral therapy is indicated in patients with conserved liver function in whom the indication for transplantation is hepatocellular carcinoma. · In patients with Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response. · Patients with Child-Pugh C cirrhosis should not be treated with the current antiviral regimen, due to a high risk of life-threatening complications. · Treatment can be started at low doses of pegylated interferon alfa and ribavirin, following a low accelerated dose regimen or at full doses. In the

Clinical Guideline	Recommendation(s)
	latter case, dose reductions and treatment interruptions are required in >50% of cases. · Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven. Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment. · There is no evidence of benefit from low dose pegylated interferon alfa maintenance therapy in patients who do not achieve an SVR. · Graft rejection is rare but may occur during pegylated interferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen upon antiviral therapy to guide treatment decisions. Treatment of special groups · Indications for HCV treatment in patients with human immunodeficiency virus (HIV) coinfection are identical to those in patients with HCV monoinfection. The same pegylated interferon alfa regimen should be used in HIV coinfected patients, but the ribavirin dose should always be weight based. · Longer treatment duration (72 weeks for genotype 1 and 48 weeks for genotypes 2 and 3) may be needed in patients with HIV coinfection. · Patients coinfected with hepatitis B should be treated with pegylated interferon alfa and ribavirin, following the same rules as monoinfected patients. · If hepatitis B virus replicates at significant levels before, during or after HCV clearance, concurrent hepatitis B virus nucleoside/nucleotide analogue therapy is indicated. · Patients on hemodialysis can be safely treated with pegylated interferon alfa monotherapy; however, combination therapy with ribavirin can be considered in select patients. · Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to transplantation due to the increased risk of acute transplant rejection. · Regular alcohol consumption should be strongly discouraged. · Treatment of patients with active illicit drug abuse has to be individualized. · Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring. Follow up of untreated patients and of nonsustained responders · Untreated patients with chronic hepatitis C and nonsustained responders should be followed regularly. · Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis. Treatment of acute hepatitis C · Pegylated interferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and obtains viral eradication in >90% of patients. · Patients failing to respond should be retreated according to the standard of care for chronic hepatitis C. Perspective of triple therapy with pegylated interferon alfa, ribavirin and protease inhibitors · New direct acting antiviral agents should be used only according to the package label.

Clinical Guideline	Recommendation(s)
	· Potential challenges should be considered when using HCV protease inhibitors in combination with pegylated interferon alfa and ribavirin and include: o Rapid emergence of drug resistance in particular in previous nonresponders, patients not fully adherent to therapy and patients not being able to tolerate optimal doses of pegylated interferon alfa and ribavirin treatment. o More strict and frequent monitoring of serum HCV RNA. o Lower response rates to triple therapy in patients with advanced liver fibrosis. o Adherence to recommended stopping rules for the antiviral agent and/or the entire treatment regimen. o Additional side effects associated with protease inhibitor treatment.
Centers for Disease Control and Prevention: **Hepatitis ABC Fact Sheet (2010)**[6]	Hepatitis C · For acute hepatitis C, antivirals and supportive treatments are used. · Regular monitoring for signs of liver disease progression is required and some patients are treated with antiviral drugs.
American Gastroenterological Association: **Medical Position Statement on the Management of Hepatitis C (2006)**[7]	· The treatment of choice is pegylated interferon plus ribavirin. · Patients with genotypes 1 and 4 require 48 weeks of therapy with pegylated interferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight). · Patients with genotypes 2 and 3 can be treated for only 24 weeks with pegylated interferon and 800 mg of ribavirin daily, with the following exceptions: · A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy. · Twelve weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week four. · Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.

Conclusions

Boceprevir (Victrelis®) and telaprevir (Incivek®) are the newest medications to be Food and Drug Administration (FDA)-approved for the treatment of adults with chronic hepatitis C genotype 1 infection.[8,9] These agents are the first to be approved in a new class of hepatitis C protease inhibitors that inhibit the replication of hepatitis C virus (HCV) host cells by binding to the nonstructural 3/4A protease of HCV genotype 1a and 1b.[8-10] According to the FDA-approved indications of these agents, boceprevir can be used in treatment naïve patients, as well as those who have failed previous interferon-based therapy. Telaprevir is also approved for use in treatment naïve patients, as well as those who have been previously treated with interferon-based treatment, including prior null responders, partial responders and relapsers. The major difference between the two FDA-approved indications is that telaprevir is appropriate for use in treatment experienced patients who were previous null responders (<2 $\log_{10}$ IU/mL decrease in HCV ribonucleic acid (RNA) at week 12 of prior treatment). Treatment experienced patients need to have demonstrated some response (nonresponder [decrease in the HCV RNA level ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a sustained virologic response (SVR)] or relapse [undetectable HCV RNA level at the end of prior therapy without subsequent attainment of a SVR]) to previous interferon-based therapy in order to be appropriate for boceprevir. Both agents must be administered in combination with the current standard of care, pegylated interferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to boceprevir and telaprevir.[8,9]

Boceprevir is added to standard therapy (pegylated interferon alfa and ribavirin) after a four week lead-in period with standard therapy alone. It is administered three times daily for either 24 or 32 weeks based on a patient's treatment history and HCV RNA levels.[8] Telaprevir can be initiated with standard therapy and is administered

three times daily for 12 weeks, regardless of treatment history of HCV RNA levels.[9] Both agents are associated with an increased risk of anemia when administered with standard therapy.[8,9] In addition, telaprevir is associated with the development of rash, which can be serious in nature.[9]

The pivotal clinical trials demonstrate that use of the hepatitis C protease inhibitors, in combination with the standard therapy, results in significantly higher SVR rates among adult patients with chronic hepatitis C genotype 1 infection compared to standard therapy alone. In select patients with satisfactory early virologic responses, the total treatment duration may be shortened (i.e., response guided treatment).[11-13,15,16] Specifically, clinical trial data demonstrates, and FDA-approved dosing states, that if a patient has an undetectable HCV RNA level at treatment weeks four and 12 with a telaprevir-containing regimen, 24 weeks of total treatment is effective in achieving a SVR. A patient with an undetectable HCV RNA level at treatment weeks eight and 24 with a boceprevir-containing regimen requires 28 or 36 weeks of total treatment depending on their previous treatment history.[8,9,11-13,15,16] Of note, standard treatment futility rules apply to any triple therapy regimen used for the treatment of chronic hepatitis C genotype 1 infection. Futility should be assessed at treatment weeks four, 12 and 24 with telaprevir-containing regimens, and at treatment weeks 12 and 24 with boceprevir-containing regimens.[8,9]

Combination treatment with pegylated interferon alfa and ribavirin remains the standard of care for the treatment of chronic hepatitis C.[3-7] The hepatitis C protease inhibitors are recommended, along with standard therapy, for the treatment of chronic hepatitis C genotype 1 infection.[4,5] Treatment guidelines do not give preference to one specific pegylated interferon alfa or ribavirin product over another.[3-7,26] Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with FDA-approved indications and dosing.[4,5,26]

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