

Drug Monograph

Brand Name: Victrelis™

Generic Name: Boceprevir

Manufacturer⁴: MERCK & CO., INC.

Drug Class^{1,2,3,4}: Protease Inhibitor, Antiviral Agent

Uses^{1,2,3,4}:

Labeled: Treatment of Chronic HCV Genotype 1 (G1) in patients with compensated liver disease (including cirrhosis)

Unlabeled: There are currently no unlabeled indications.

Mechanism of Action^{1,2,3,4}: Boceprevir is a direct-acting Hepatitis C Virus (HCV) nonstructural (NS) 3/4A inhibitor. It binds to the NS3 protease active site, in HCV genotype 1a and 1b, forming a reversible covalent bond inhibiting HCV NS3/4A protease. The NS3/4A protease is responsible for proteolytic cleavage of the HCV encoded polyprotein producing the mature forms necessary for viral reproduction.

Pharmacokinetics^{1,2}:

Absorption:

Table 1:

Tmax	2 hours
Vd	~772L
t _{1/2}	~3 hours
Cl	161 L/hour
Protein Binding	~75%
Bioavailability*	unknown

*Food increases absorption and bioavailability by up to 6

Metabolism:

Boceprevir is metabolized to inactive ketone-reduced metabolites in the liver via the aldoketoreductase-mediated pathway. It is also oxidized via CYP3A4/5.

Elimination:

Boceprevir is eliminated via the kidney (9% with 3 % unchanged) and feces (79% with 8% unchanged).

Efficacy:

Poordad F, McCone J, Bacon BR, Bruno S, Manns M, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* [serial online]. 2011; 364 (13): 1195-1206.

Study Design: Phase 3, international, randomized, placebo-controlled study

Description of study: *Methods:* One-thousand-two-hundred-forty-six nonblack and two-hundred-twenty-six black patients were screened for their respective cohort, of whom nine-hundred-forty and one-hundred-fifty-nine met selection criteria and were randomly assigned to one of three treatment groups. The study consisted of a 4-week lead-in period with peginterferon alfa and ribavirin for all treatment groups. Study group one then received peginterferon-ribavirin for 44 weeks with a three times daily placebo. Study group two received response guided therapy and boceprevir three times a day for a total of 24 week. If HCV RNA levels were undetectable between weeks 8 and 24, treatment was considered complete, but, if HCV RNA levels were detectable at any point between weeks 8 and 24 (not including week 24), peginterferon-ribavirin was continued and placebo administered for weeks 28 through 48. Study group 3 received fixed-duration therapy. They received peginterferon-ribavirin with boceprevir three times daily for 44 weeks after the lead-in period. In all three groups, if a detectable HCV RNA level was detectable at week 24, treatment was discontinued. Efficacy and safety were determined through measure of plasma HCV RNA levels and grading of adverse events by investigators. *Outcome Results:* In the nonblack cohort, response at end of therapy was 57%, 74% and 77% and the sustained virologic response was 40%, 67%, and 68% for groups 1, 2 and 3 respectively. In the black cohort, response at end of therapy was 29%, 50%, and 65% and the sustained virologic response was 23%, 42%, and 53% for groups 1, 2 and 3 respectively. The rates of response at end of therapy and sustained virologic response for group 2 and 3 were similar for both the nonblack and black cohort. Adverse events occurred in greater than 98% of study patients. The most common being fatigue, headache, and nausea. Serious adverse events were seen in 9%, 11% and 12% of patients with respect to groups 1, 2 and 3. Dysgeusia and anemia were reported nearly twice as often in the study groups receiving boceprevir. Patient's experiencing anemia more frequently required dose reductions if they were receiving boceprevir (13% v 21%) and were administered erythropoietin more frequently (24% v 43%).

Limitations: This study was funded by Schering-Plough [now Merck] and 13 of the 15 listed authors of the study reported receiving fees from Merck or Schering-Plough. Schering-Plough is the manufacturer of boceprevir. This presents multiple conflicts of interest. The large difference in adverse events may have resulted in un-blinding from both sides of the study. Potential of un-blinding was not determined for this study. This trial excluded patients that had previously been treated for HCV as well as patients with co-infections of HBV and/or HIV, inhibiting extrapolation of this study to a significant population of patients with HCV.

Conclusion: This study showed that boceprevir is a successful adjunct therapy for previously untreated chronic HCV genotype 1 infection, but has a considerable increase in serious adverse effects. However, it did not establish efficacy in patients with chronic

HCV genotype 1 infection that have been previously treated, limiting some of its applicability in the treatment of HCV genotype 1 infection. More studies need to be done to determine the impact of the increase in serious adverse events on the patients.

Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med [serial online]. 2011; 364 (13): 1207-1217.

Study Design: International, randomized, open-label, placebo-controlled study

Description of study: *Methods:* Six-hundred-forty patients with chronic HCV genotype 1 infection were evaluated for enrollment in the study, with four-hundred-three being enrolled and undergoing randomization in a 1:2:2 ratio between treatment groups, with a primary efficacy endpoint of sustained virologic response defined as patients that either had non-response or relapse. Peginterferon alfa-2b was dosed at 1.5µg per kilogram once weekly and a daily divided dose of ribavirin at 600 to 1400mg per day based on body weight. Treatment with boceprevir consisted of 800mg three times a day (taken with food 7-9 hours apart). A lead-in of peginterferon-ribavirin of 4 weeks was given to each group. Group 1, the control, then received placebo and peginterferon-ribavirin for a 48 week course. Group 2 received response-guided therapy with peginterferon-ribavirin and boceprevir. If HCV RNA levels were undetectable, therapy was stopped at week 36. If RNA levels were detectable at week 8 (but undetectable at week 12), placebo and peginterferon-ribavirin was continued until week 48. Group 3 received boceprevir and peginterferon-ribavirin for 44 weeks after the lead-in. For any patient not achieving an undetectable HCV RNA level by week 12, therapy was discontinued. Efficacy was determined by sustained virologic response and safety was determined by grading of adverse events by investigators using the modified World Health Organization grading system. *Outcome Results:* Race, mean age, and gender were similar across all groups. The overall rate for the primary efficacy endpoint, of sustained virologic response, for groups 1, 2, and 3 were 21%, 59%, and 66% respectively. Subgroup analyses showed patients with a prior relapse had rates of sustained virologic response of 29%, 69% and 75% with respect to groups 1, 2, and 3. Patients with a previous poor response to interferon experienced a sustained virologic response in 33% and 34 % with respect to groups 2 and 3. No patients in the control group identified as a having a poor response achieved a sustained virologic response. In patients defined as having a good response to interferon, 25% of group 1, 75% of group 2 and 79% of group 3 achieved a sustained virologic response. In the boceprevir groups, a greater amount of patients experienced serious adverse events. Anemia occurred in groups 1, 2 and 3 at a rate of 20%, 43%, and 46%, respectively. Dysgeusia was experienced by 11%, 43% and 45% with respect to groups 1, 2 and 3.

Limitations: This study was funded by Schlering-Plough [now Merck], the manufacturer of boceprevir. There is no declaration of the author's affiliations with any drug manufacturers, but it appears likely. Possible un-blinding could have occurred by both patients and investigators through a large difference in adverse effects associated with the boceprevir groups. Potential for un-blinding was not determined for this study.

Conclusions: Boceprevir in combination with peginterferon and ribavirin increased the rate of sustained virologic response. However, there was an increased rate of serious adverse effects (anemia, neutropenia) in the treatment groups receiving boceprevir. More studies examining the cost associated with the treatment and decrease in quality of life due to the serious side effects need to be done to determine the impact on the patient.

Kwo PY, Lwitez EJ, McCone J, Schiff ER, Vierling JM, Pound D, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet [serial online]. 2010; 376 (9742): 705-716.

Study Design: Open-label, randomized, multicenter active-control trial

Description of study: *Methods:* Seven-hundred-sixty-five patients with previously untreated genotype 1 HCV were screened with five-hundred-ninety-five patients being enrolled. In part 1, participants were randomized into one of five treatment groups in a 1:1:1:1:1 ratio and stratified by race (black vs nonblack) and cirrhosis status (cirrhosis vs no cirrhosis). Peginterferon alfa-2b and ribavirin were dosed at 1.5µg/kg and 800-1400mg/day for all groups in part 1. Treatment for groups was as follows: Group 1 received peginterferon-ribavirin for 48 weeks, Group 2 received a lead-in of peginterferon-ribavirin for 4 weeks and boceprevir 800mg three times a day to complete 28 days of therapy, Group 3 also received a lead-in of four weeks and then boceprevir was added to complete a 48 week course, Groups 4 and 5 received boceprevir from the beginning of therapy and received 24 and 48 weeks of therapy respectively. Adverse event were graded as mild, moderate, and severe. Dose adjustments were made as necessary and treatment of adverse effects was at the discretion of the investigator. The primary endpoint for this trial was sustained virologic response (SVR) defined as the proportion of patients with undetectable HCV RNA levels 24 weeks after discontinuation of therapy. *Outcome Results:* Statistical and safety analyses were based on an intent-to-treat model. All boceprevir treatment groups showed improvement over the control group, SVRs were 38%, 56%, 75%, 54%, and 67% with respect to groups 1, 2, 3, 4, and 5. They found that patients of African-American descent or with cirrhosis achieved a lower SVR in the control group than treatment groups (13% vs 53% and 25% vs 67% respectively). The most frequent adverse effects of treatment were fatigue, anemia, nausea, and headache. Anemia was more frequently observed in treatment groups receiving boceprevir and required epoetin alfa at a higher rate. Anemia (Nadir hemoglobin <100) was reported in 48%, 67%, 88%, 61%, and 79% with respect to groups 1, 2, 3, 4, and 5.

Limitations: This trial was an open-label trial financed by Merck, with many of the authors receiving benefit/funds directly from the company. This presents a conflict of interest as Schering-plough, a subsidiary of Merck, manufactures boceprevir. It was an open-label trial. This trial did not include patients that had previously been treated and either had a poor response or failure to therapy, limiting applicability of the study to that population of patients. It did not include patients over the age of 60.

Conclusions: This trial showed a significant increase in SVR in patients treated with boceprevir. It was an open-label trial but the results were statistically and potentially clinically significant. Double-blind trials comparing standard of care to boceprevir should be completed to determine boceprevir's place in therapy.

Contraindications^{1,2,3,4}:

- Women who are or may become pregnant and male partners of pregnant woman
- Concomitant use of cytochrome P-450 (CYP) isoenzyme 3A4/5 substrates in which elevated plasma concentrations would likely cause a serious or life-threatening event
- Concomitant use of potent CYP isoenzyme 3A4/5 inducers that may reduce boceprevir plasma concentrations and result in loss of virologic response

Precautions^{1,2,3,4}:

- Further decreases in hemoglobin concentrations have been reported with the addition of boceprevir to peginterferon alfa and ribavirin therapy, requiring monitoring and possible modification in dose of ribavirin or discontinuation of therapy
- Neutropenia may worsen with the addition of boceprevir to peginterferon alfa and ribavirin therapy, requiring monitoring and possible dose modification of peginterferon alfa and/or ribavirin or discontinuation of therapy

Adverse effects^{1,2,3,4}:

Common

Dermatological: Alopecia (22% to 27%), Dry skin (18% to 22%), Rash (16% to 17%)

Gastrointestinal: Nausea (43% to 46%), Altered taste (35% to 44%), Diarrhea (24% to 25%), Loss of appetite (25% to 26%), Vomiting (15% to 20%), Xerostomia (11% to 15%)

Musculoskeletal: Arthralgia (19% to 23%), Weakness (15% to 21%)

Neurological: Fatigue (55% to 58%), Insomnia (30% to 34%), Irritability (21% to 22%), Asthenia (15% to 21%), Dizziness (16% to 19%), Headache

Other: Shivering (33% to 34%)

Serious

Hematological: Anemia (45% to 58%), Neutropenia (14% to 25%), Thrombocytopenia (1% to 4%)

Drug Interactions^{1,2,3}:

CYP 3A4/5 Substrates

Boceprevir is a strong inhibitor of CYP3A4/5 and may result in increased levels of CYP3A4/5 substrates.

Alfuzosin, alprazolam, amiodarone, atorvastatin, bepiridil, bosentan, budesonide, cisepride, clarithromycin, colchicine, cyclosporine, dihydroergotamine, ergonovine, ergotamine, felodipine, fesoterodine, fluticasone, itraconazole, lovastatin, methylergonovine, midazolam, nicardipine, nifedipine, pimozide, propafenone, quinidine, ruxolitinib, salmeterol, simvastatin, sirolimus, sunitinib, tacrolimus, trazodone, vardenafil, voriconazole

CYP 3A4/5 Inducers

Boceprevir is partially metabolized by the CYP3A4/5 isoenzyme and plasma levels of boceprevir may be decreased.

Carbamezipine, dexamethasone, phenobarbital, phenytoin, rifampin, St. John's Wort

CYP3A4/5 Inhibitors

Boceprevir is partially metabolized by CYP3A4/5 isoenzyme and plasma levels of boceprevir may be increased

Itraconazole, ketoconazole, posiconazole, voriconazole

P-glycoprotein inhibitors or substrates

Boceprevir is a substrate for P-glycoprotein and a potential inhibitor.

Antiarrhythmic Agents

May result in increased concentrations of antiarrhythmic agents (amiodarone, flecainide, propafenone, quinidine). If boceprevir and antiarrhythmic agents are used, use caution and monitor the antiarrhythmic agent's plasma concentrations.

Buprenorphine

Potential pharmacokinetic interaction exists resulting in altered concentrations of buprenorphine. Dosage adjustments of buprenorphine may be necessary.

Desipramine

May result in increased desipramine plasma concentrations and may lead to increase in desipramine adverse effects.

Digoxin

May result in increased digoxin plasma concentrations. Close monitoring of serum digoxin concentrations is recommended with titration of digoxin dose as necessary.

Drospirenone

Results in increased drospirenone levels leading to an increased risk of hyperkalemia, co-administration is contraindicated.

Efavirenz

Pharmacokinetic interaction exists resulting in decreased boceprevir concentrations and AUC. Co-administration may result in loss of therapeutic effects and should be avoided.

Ethinyl Estradiol

May result in decreased concentrations of ethinyl estradiol causing failure of birth control

Methadone

Co-administration results in fluctuations in methadone plasma concentrations. Close monitoring is recommended and dosage adjustments of methadone may be necessary.

Rifabutin

Potential pharmacokinetic interaction exists resulting in possible increases in exposure to rifabutin and decreased concentrations of boceprevir.

Ritonavir

Pharmacokinetic interaction with low-doses occurs resulting in decreased concentrations and AUC of boceprevir. Possible effect on therapy is unknown.

Sildenafil

Co-administration results in increased sildenafil concentrations with increased risk of serious adverse effects (i.e. hypotension, priapism, syncope)

Tadalafil

Co-administration resulted in increased tadalafil concentrations with increased risk for serious adverse effects (i.e. hypotension, priapism, syncope)

Warfarin

Potential pharmacokinetic interaction exists. If co-administration is required close monitoring of INR is recommended.

Dosing/Administration^{1,2,3,4}:

Usual Adult Dose: 800mg orally three times a day (every 7 to 9 hours) with food (in combination with peginterferon alfa (PA) and ribavirin(R))

Recommended treatment regimens:

Table 2:

Patient Type	Response at weeks 8 and 24 (HCV RNA Levels)	Response Guided Therapy	Total Duration of Therapy
Treatment-naïve	Undetectable/undetectable	Weeks: 1-4 PA+R Weeks: 5-28 Boceprevir+PA+R	28 weeks
Treatment-naïve	Detectable/undetectable	Weeks: 1-4 PA+R Weeks: 5-36 Boceprevir+PA+R Weeks: 36-48 PA+R	48 weeks
Partial response or Relapse	Undetectable/undetectable	Weeks: 1-4 PA+R Weeks: 5-36 Boceprevir+PA+R	36 weeks

Partial response or Relapse	Detectable/undetectable	Weeks: 1-4 PA+R Weeks: 5-36 Boceprevir+PA+R Weeks: 36-48 PA+R	48 weeks
Compensated Cirrhosis	Undetectable or detectable/undetectable	Weeks: 1-4 PA+R Weeks: 5-48 Boceprevir+PA+R	48 weeks

Pediatric dose: Boceprevir's safety and efficacy has not been established in pediatric patients

Dosing in renal impairment: Dosage adjustment not required with any degree of renal impairment

Dosing in hepatic impairment: In mild, moderate, or severe impairment, no dosage adjustment is required

Use in special circumstances^{1,2,3,4}:

- Pregnancy category: B (all trimesters). However, boceprevir must be used in combination with peginterferon alfa (Category: C) and ribavirin (Category: X). Therefore, use in women who are pregnant or may become pregnant and men of partners who are pregnant is contraindicated.
- Geriatric Use: Boceprevir has not been studied in patients ≥ 65 years of age.

Conclusion: Boceprevir is an effective adjunct treatment to the current standard of care of peginterferon alfa with ribavirin for chronic HCV genotype 1 infection. It shows treatment efficacy in both treatment-naïve patients as well as patients with treatment failure or poor response to prior treatment. It does have a significant side effect profile with anemia and neutropenia rates being higher with boceprevir compared to the standard of care. Costs associated with treatment of side effects were not discussed in any study but should be included as a secondary objective in future studies. There are multiple drug interactions with this medication as it is an inhibitor and substrate of CYP 3A4/5. Each patient receiving treatment for HCV genotype 1 should have their risks vs benefits weighed individually prior to initiation of adjunct therapy with boceprevir. With respect to the large increase in sustained virologic response in both treatment-naïve and previously treated patients, the clinical benefit of this medication may outweigh the risk of side effects and drug interactions that may occur in both treatment naïve patients and patients with relapse or poor response to initial therapy.

References:

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7. Kwo PY, Lwitez EJ, McCone J, Schiff ER, Vierling JM, Pound D, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* [serial online]. 2010; 376 (9742): 705-716. Available from: www.sciencedirect.com. Accessed January 10, 2012.

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