PRODUCT MONOGRAPH

VICTRELIS™

boceprevir

200 mg capsule

Hepatitis C Virus (HCV) Protease Inhibitor

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Date of Preparation:
July 27th, 2011

Submission Control No: 141556

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VICTRELIS™

boceprevir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
oral	capsules / 200 mg	lactose monohydrate *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

VICTRELIS™ (boceprevir) is indicated for: The treatment of Chronic Hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alpha (PegIFNα)/ribavirin (RBV), in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous therapy.

This indication is based on evidence from two Phase 3 clinical studies conducted with VICTRELIS™ in combination with peginterferon alfa-2b (PegIFNα2b)/RBV, SPRINT-2 in previously untreated patients and RESPOND-2 in previous treatment failures. Previous null responders (defined by a < 2.0 $\log_{10}$ decline in HCV-RNA at Treatment Week (TW) 12) were excluded from the RESPOND-2 study. However, the results of the Phase 3 studies included a post-hoc analysis of a population similar to Null Responders (defined as poorly interferon responsive at TW 4 [< 1.0 $\log_{10}$ decline in HCV-RNA]) (see **CLINICAL TRIALS**).

Treatment with VICTRELIS™ should be initiated and monitored by a physician experienced in the management of CHC. Before initiating therapy, the following points should be considered:

- VICTRELIS™ must not be used as a monotherapy but only in combination with PegIFNα/RBV.

- VICTRELIS™ efficacy has not been studied in patients who have failed previous therapy regimens which included VICTRELIS™ or other HCV NS3/4A Protease Inhibitors (PIs).

- Poorly interferon responsive patients who were treated with VICTRELIS™ in combination with PEGETRON® (PegIFNα2b/RBV) achieved lower Sustained Virologic Response (SVR) and higher rate of resistance associated substitutions upon treatment failure compared to patients with a greater response to PEGETRON® (see **CLINICAL TRIALS** and **MICROBIOLOGY**, **Resistance**).

Geriatrics (> 65 years of age)
Clinical studies of VICTRELIS™ included only a limited number of patients aged 65 and over. Consideration should be given to the decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy in elderly patients prior to prescribing VICTRELIS™ (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (< 18 years of age)
No data is available (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS

VICTRELIS™, in combination with PegIFNα/RBV (refer to the PegIFNα/RBV Product Monographs for additional information), is contraindicated in:

Patients with known hypersensitivity to boceprevir (BOC) or to any of the ingredients of the product (including the capsule). For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

Patients with autoimmune hepatitis.

Patients with hepatic decompensation (Child-Pugh score > 6 [class B and C]).

Pregnant women and men whose female partners are pregnant (see **WARNINGS AND PRECAUTIONS**).

Co-administration with medicines that are highly dependent on CYP3A4/5 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These drugs are listed in Table 1 (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

Co-administration with medicines that are potent CYP3A4/5 inducers, where significantly reduced BOC plasma concentrations may be associated with reduced efficacy. These drugs are listed in Table 1 (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

Table 1: Drugs that are contraindicated with boceprevir

Drug Class/Drug Name	Clinical Comment
Alpha 1-Adrenoreceptor Antagonists alfuzosin	Increased alfuzosin concentrations can result in hypotension.
Antiarrhythmics amiodarone, propafenone, quinidine	Potential to produce serious and/or life-threatening Adverse Events (AEs).
Anticonvulsants carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response to VICTRELIS™.
Antimycobacterials rifampin	May lead to loss of virologic response to VICTRELIS™.

Drug Class/Drug Name	Clinical Comment
Ergot Derivatives dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal Motility Agents cisapride[a]	Potential for cardiac arrhythmias.
Herbal Products St. John's Wort (hypericum perforatum)	May lead to loss of virologic response to VICTRELIS™.
HMG-CoA Reductase Inhibitors lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis.
Neuroleptics pimozide	Potential for cardiac arrhythmias.
Oral Contraceptives drospirenone	Potential for hyperkalemia.
PDE-5 Enzyme Inhibitors sildenafil or tadalafil when used for the treatment of Pulmonary Arterial Hypertension (PAH)	Potential for PDE5 inhibitor-associated AEs, including visual abnormalities, hypotension, prolonged erection, and syncope.
Second Generation Antihistamines astemizole[a], terfenadine[a]	Potential for cardiac arrhythmias.
Sedatives/Hypnotics midazolam (orally administered), triazolam (orally administrated)	Potential for prolonged or increased sedation or respiratory depression.

a: Please note that cisapride, astemizole and terfenadine are no longer available on the Canadian market.

The prescribing information of both PegIFNα and RBV should be consulted before treatment with VICTRELIS™.

WARNINGS AND PRECAUTIONS

General

Effects on Ability to Drive and Use Machines

No studies on the effects of VICTRELIS™ in combination with PegIFNα/RBV on the ability to drive and use machines have been performed. However, certain side effects that have been reported may affect some patients' ability to drive and operate machinery. Patients should be informed that fatigue, dizziness, syncope, blood pressure fluctuations and blurred vision have been reported (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Reactions**).

Hematologic

Anemia

Anemia has been reported with PegIFNα/RBV therapy. The addition of VICTRELIS™ to PEGETRON® is associated with an additional decrease in serum hemoglobin concentrations (approximately 10 g/L) (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Reactions, Anemia** and **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**).

Refer to the RBV Product Monographs for statements regarding dose reduction and/or interruption.

Neutropenia
Neutropenia is a known interferon-related AE. In Phase 2 and 3 clinical trials, the proportion of subjects with neutrophil counts of less than 0.5 x 10^9/L was higher in the VICTRELIS™-containing arms (7 %) compared to patients who received only PEGETRON® (4 %) (see **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings, Neutrophils and Platelets**). In the key clinical trials, three patients experienced severe (2) or life-threatening (1) infections within 14 days of Grade 3 or 4 neutropenia and two patients experienced life-threatening neutropenia while receiving the combination of VICTRELIS™ with PEGETRON®.

Refer to the PegIFNα Product Monographs for statements regarding dose reduction and/or discontinuation.

Sensitivity/Resistance
Hepatitis C Virus Protease Monotherapy
Based on results of clinical studies, VICTRELIS™ must not be used alone due to the high probability of increased resistance without combination anti-HCV therapies (see **MICROBIOLOGY**, **Resistance**).

It is unknown what effect therapy with VICTRELIS™ will have on the activity of subsequently administered HCV NS3/4A Protease Inhibitors (PIs), including re-treatment with VICTRELIS™.

Sexual Function/Reproduction
Effects on Fertility
No human data on the effect of VICTRELIS™ on fertility are available. Available pharmacodynamic/toxicological data in rats have shown effects of BOC/metabolites on fertility, which have been reversible (female rats) and partially reversible (male rats) (see **TOXICOLOGY**).

Special Populations
Pregnant Women
Because VICTRELIS™ must be used in combination with PegIFNα/RBV, the **CONTRAINDICATIONS AND WARNINGS** applicable to those drugs are applicable to combination treatment. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to RBV, and interferons have been shown to have abortifacient effects in animals. Refer to the prescribing information for PegIFNα/RBV for full details.

Because of these risks, VICTRELIS™, in combination with PegIFNα/RBV, is contraindicated in pregnant women and men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients while taking this combination – both during treatment and for 6 months after the completion of all treatment. Combination therapy should not be started unless a female patient has a negative pregnancy test immediately prior to initiation of treatment and routine monthly pregnancy tests during treatment and for 6 months after all treatment has ended.

Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS™ (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**). Therefore, two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with VICTRELIS™ and concomitant PegIFNα/RBV.

There are no studies with VICTRELIS™ in pregnant women.
No effects on fetal development have been observed in rats and rabbits at BOC AUC exposures approximately 11.8- and 2.0-fold higher, respectively, than those in humans at the recommended dose of 800 mg Three Times Daily (TID). BOC has been shown in animals to distribute across the placenta to fetal blood and tissues (see **TOXICOLOGY**).

Nursing Women
A decision must be made whether to discontinue nursing or discontinue treatment with VICTRELIS™ taking into account the potential for adverse reactions from the drug in nursing infants and the benefit of therapy for the mother.

Available pharmacodynamic/toxicological data in animals have shown excretion of BOC and/or metabolites in milk (see **TOXICOLOGY**). Consequently a risk to nursing newborns/infants cannot be excluded.

Pediatrics (< 18 years of age)
The safety, efficacy and Pharmacokinetic (PK) profile of VICTRELIS™ in pediatric patients below 18 years of age have not yet been established.

Geriatrics (> 65 years of age)
Clinical studies of VICTRELIS™ had limited data on patients aged 65 and over to determine whether they respond differently from younger patients. In general, consideration should be given to the potentially decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy in elderly patients (see **DETAILED PHARMACOLOGY**).

Human Immunodeficiency Virus (HIV) Co-infection
The safety and efficacy of VICTRELIS™ alone or in combination with PegIFNα/RBV for the treatment of CHC genotype 1 infection have not been established in patients co-infected with HIV and HCV.

Hepatitis B Virus (HBV) Co-infection
The safety and efficacy of VICTRELIS™ alone or in combination with PegIFNα/RBV for the treatment of CHC genotype 1 infection in patients co-infected with HBV and HCV have not been studied.

Organ Transplant Recipients
The safety and efficacy of VICTRELIS™ alone or in combination with PegIFNα/RBV for the treatment of CHC genotype 1 infection in liver or other organ transplant recipients have not been studied.

Monitoring and Laboratory Tests

HCV-RNA levels should be monitored at Treatment Weeks (TWs) 8, 12, and 24, at the End of Treatment (EOT), during treatment follow-up, and for other time points as clinically indicated. In previously untreated subjects without cirrhosis, monitoring of HCV-RNA levels at TW 4 is recommended to determine interferon responsiveness. Use of a sensitive real-time reverse-transcription polymerase chain reaction (RT-PCR) assay for monitoring HCV-RNA levels during treatment is recommended. The assay should have a lower limit of HCV-RNA quantification of equal to or less than 25 IU/mL, and a limit of HCV-RNA detection of approximately 10-15 IU/mL. For the purposes of assessing Response-Guided Therapy (RGT) milestones, a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA result.

Complete blood counts (with white blood cell differential counts) should be obtained before treatment, at TWs 4, 8 and 12 and should be closely monitored at other time points as considered clinically appropriate. If serum hemoglobin is < 100 g/L, a decrease in dose or interruption of RBV may be warranted (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Reactions, Anemia**). Decreases in the neutrophil counts may require dose reduction or discontinuation of PegIFNα/RBV (see **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**).

Refer to the PegIFNα/RBV Product Monographs for directions regarding dose reduction or discontinuation.

Refer to the prescribing information of PegIFNα/RBV, including pregnancy testing requirements.

ADVERSE REACTIONS

Adverse Drug Reaction (ADR) Overview

The following serious and otherwise important ADRs are discussed in detail in another section of the labelling: Anemia and Neutropenia (see **WARNINGS AND PRECAUTIONS**).

The most commonly reported adverse reactions were similar across all study arms. The most commonly reported adverse reactions (incidence > 35 %) considered by investigators to be causally related to the combination of VICTRELIS™ with PEGETRON® in adult patients in clinical trials were fatigue, anemia, nausea, headache, and dysgeusia.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse Drug Reaction information from clinical trials is useful for identifying drug-related AEs and for approximating rates.

The safety of the combination of VICTRELIS™ 800 mg TID with PEGETRON® was assessed in 2,095 patients with CHC in one Phase 2, open-label trial and two Phase 3, randomized, double-blind, placebo-controlled clinical trials. The Phase 2 study SPRINT-1 (P03523) evaluated the use of VICTRELIS™ in combination with PEGETRON® with or without a four-

week lead-in period with PEGETRON® compared to PEGETRON® alone in patients who were previously untreated. The Phase 3 studies SPRINT-2 (P05216 – patients who were previously untreated) and RESPOND-2 (P05101 – patients who had failed previous therapy) evaluated the use of VICTRELIS™ 800 mg TID in combination with PEGETRON® with a four-week lead-in period with PEGETRON® alone compared to PEGETRON® alone (see **CLINICAL TRIALS**). The population studied had a mean age of 49 years (2 % of patients were > 65 years of age), 61 % were male, 82 % were White and 15 % Black, and 7 % of the population had cirrhosis (based on liver histology). In the pooled studies, the median exposure was 201 days in patients who received VICTRELIS™ in combination with PEGETRON® and 198 days in patients who received PEGETRON® alone.

During the four-week lead-in period with PEGETRON® alone, 2 % (28/1,263) patients in the VICTRELIS™-containing arms experienced adverse reactions leading to discontinuation of treatment. During the entire course of treatment, the proportion of patients who discontinued treatment due to adverse reactions was 13 % for patients who received the combination of VICTRELIS™ with PEGETRON® and 12 % for patients who received PEGETRON® alone. Events resulting in discontinuation were similar to those seen in previous studies with PEGETRON®. Only anemia and fatigue were reported as events that led to discontinuation in > 1 % of patients in any arm.

Adverse reactions that led to dose modifications of any medication (primarily PEGETRON®) occurred in 39 % of patients who received the combination of VICTRELIS™ with PEGETRON® compared to 24 % of patients who received PEGETRON® alone. The most common reason for dose reduction was anemia, which occurred more frequently in patients who received the combination of VICTRELIS™ with PEGETRON® than in patients who received PEGETRON® alone.

Adverse reactions were considered by investigators to be causally related to the combination of VICTRELIS™ with PEGETRON®. Adverse reactions reported in ≥ 4 % of patients who received the combination of VICTRELIS™ with PEGETRON® and reported at a greater rate than the PEGETRON® in SPRINT-1, SPRINT-2, and RESPOND-2 are listed by System Organ Class in Table 2.

Table 2: Treatment-related Adverse Reactions Reported in ≥ 4 % of Patients who received the Combination of VICTRELIS™ with PEGETRON® and Reported at a Greater Rate than PEGETRON® alone[a, b]

Adverse Reactions	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Patients Reporting Adverse Reactions		Patients Reporting Adverse Reactions	
Body System Organ Class	BOC/PegIFNα2b/ RBV n = 1,225 (%)	PegIFNα2b/RBV n = 467 (%)	BOC/PegIFNα2b/ RBV n =323 (%)	PegIFNα2b/RBV n = 80 (%)
Median Exposure (days)	**197**	**216**	**253**	**104**
Blood and Lymphatic System Disorders				
Anemia	50	30	45	20
Leukopenia	9	8	5	1
Neutropenia	25	19	14	10
Thrombocytopenia	4	1	3	0
Eye Disorders				

Adverse Reactions	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Patients Reporting Adverse Reactions		Patients Reporting Adverse Reactions	
Body System Organ Class	**BOC/PegIFNα2b/ RBV n = 1,225 (%)**	**PegIFNα2b/RBV n = 467 (%)**	**BOC/PegIFNα2b/ RBV n =323 (%)**	**PegIFNα2b/RBV n = 80 (%)**
Vision Blurred	7	5	2	1
Gastrointestinal Disorders				
Abdominal Pain	5	4	3	9
Abdominal Pain Upper	7	7	6	3
Constipation	6	5	8	5
Diarrhea	23	19	23	15
Dry Mouth	10	9	14	9
Dysgeusia	35	16	44	11
Dyspepsia	7	7	6	5
Gastroesophageal Reflux Disease	5	2	5	0
Nausea	45	40	41	38
Stomatitis	4	3	4	3
Vomiting	19	12	13	8
General Disorders and Administration Site Conditions				
Asthenia	15	18	21	16
Chills	33	29	33	30
Fatigue	58	58	55	50
Pain	10	8	7	4
Pyrexia	32	32	28	21
Investigations				
Decreased Weight	11	12	11	9
Metabolism and Nutrition Disorders				
Decreased Appetite	25	24	25	16
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	17	21	14
Back Pain	6	6	6	4
Muscle Spasms	3	3	4	3
Nervous System Disorders				
Dizziness	18	14	16	10
Headache	45	42	40	48
Memory Impairment	4	5	5	4
Paresthesia	4	2	3	1
Psychiatric Disorders				
Anxiety	13	12	12	6
Depression	23	22	16	15
Insomnia	33	33	29	20
Irritability	22	23	21	13
Mood Altered	4	3	2	3
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	18	22	23	16
Dyspnea	27	23	33	21
Epistaxis	3	2	5	3
Skin and Subcutaneous (SC) Tissue Disorders				
Alopecia	27	27	22	16
Dry Skin	17	18	22	8
Pruritus	24	25	21	18

Adverse Reactions	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Patients Reporting Adverse Reactions		Patients Reporting Adverse Reactions	
Body System Organ Class	**BOC/PegIFNα2b/ RBV n = 1,225 (%)**	**PegIFNα2b/RBV n = 467 (%)**	**BOC/PegIFNα2b/ RBV n =323 (%)**	**PegIFNα2b/RBV n = 80 (%)**
Rash	18	20	16	5
Rash Maculo-papular	4	3	3	0
Rash Papular	5	3	1	0

BOC = boceprevir; PegIFNα2b = peginterferon alfa-2b; RBV = ribavirin

a: Since VICTRELIS™ is prescribed with PegIFNα/RBV, please refer to the Product Monographs for PegIFNα/RBV for additional information.

b: Injection-site reactions have not been included since VICTRELIS™ is administered orally.

Serious Adverse Drug Reactions

Serious AEs were reported in 11 % of patients who received the combination of VICTRELIS™ with PEGETRON® and 8 % of patients who received PEGETRON®.

There were eight patient deaths that occurred during the treatment or follow-up in these clinical trials. Four deaths occurred in patients who received PEGETRON® alone (4/547, 1 %), and 4 deaths occurred in the patients who received the combination of VICTRELIS™ with PEGETRON® (4/1548, < 1 %).

Anemia

Anemia was observed in 49 % of patients treated with the combination of VICTRELIS™ with PEGETRON® compared with 29 % of patients treated with PEGETRON® alone. With the interventions used for anemia management in the clinical trials, the average additional decrease of hemoglobin was approximately 10 g/L when VICTRELIS™ was added to PEGETRON®. The mean decreases in hemoglobin values from baseline were larger in previously treated patients compared to patients who had never received prior therapy.

Dose modifications (generally of PEGETRON®) due to anemia/hemolytic anemia occurred twice as often in patients treated with the combination of VICTRELIS™ with PEGETRON® (26 %) compared to PEGETRON® alone (13 %). The proportion of patients who discontinued study drug due to anemia was low (1 % in both arms). The proportion of patients who received a transfusion for the management of anemia was 3 % of patients in the VICTRELIS™-containing arms compared to < 1 % of patients who received PEGETRON® alone. Although not approved for the treatment of anemia associated with Hepatitis C, the use of Erythropoiesis Stimulating Agents (ESAs) was permitted for management of anemia, at the investigator's discretion, with or without RBV dose reduction in the Phase 2 and 3 clinical trials. The proportion of subjects who received an ESA was 43 % in the VICTRELIS™-containing arms compared to 24 % in the PEGETRON® arm.

Clinical Trial Adverse Drug Reactions (≥ 1 % - < 4 %)

Adverse reactions reported in < 4 % and ≥1 % of patients who received the combination of VICTRELIS™ with PEGETRON® and reported at a greater rate than the PEGETRON® arms in SPRINT-1, SPRINT-2, and RESPOND-2 are listed. The incidence of the adverse reaction in previously untreated patients and previous treatment failure patients who received VICTRELIS™ with PEGETRON® reported in the parentheses following each reaction.

Cardiac Disorders: Tachycardia (1 %, 1 %)

Ear and Labyrinth Disorders: Tinnitus (3 %, 2 %)

Endocrine Disorders: Hypothyroidism (3 %, 2 %)

Eye Disorders: Retinal exudates (1 %, 1 %), and vision impairment (2 %, 1 %)

Gastrointestinal Disorders: Abdominal discomfort (3 %, 2 %), abdominal distention (1 %, 2 %), anorectal discomfort (1 %, 1 %), aphthous stomatitis (3 %, 2 %), cheilitis (2 %, 1 %), flatulence (2 %, 2 %), gingivitis (< 1 %, 2 %), glossodynia (2 %, 2 %), hemorrhoids (2 %, 1 %), mouth ulceration (2 %, 2 %), oral pain (2 %, 1 %), tongue ulceration (1 %, 2 %), and tooth disorder (1 %, 3 %)

General Disorders and Administration Site Conditions: Chest pain (2 %, 1 %), feeling of body temperature change (< 1 %, 1 %), malaise (2 %, 2 %), and mucosal dryness (1 %, 2 %)

Infections and Infestations Disorders: Cellulitis (1 %, 1 %), herpes simplex (2 %, 2 %), influenza (1 %, 1 %), oral fungal infection (2 %, 3 %), sinusitis (2 %, 1 %), and urinary tract infection (1 %, 1 %)

Metabolism and Nutrition Disorders: Dehydration (1 %, 1 %), and hypertriglyceridemia (1 %, 1 %)

Musculoskeletal and Connective Tissue Disorders: Neck pain (1 %, 2 %)

Nervous System Disorders: Amnesia (1 %, < 1 %), hypoesthesia (2 %, 1 %), parosmia (1 %, 3 %), and syncope (1 %, 2 %)

Psychiatric Disorders: Affect lability (3 %, 2 %), aggression (1 %, 1 %), anger (1 %, 2 %), confusional state (1 %, < 1 %), libido disorder (2 %, 2 %), and suicidal ideation (1 %, 1 %)

Renal and Urinary Disorders: Pollakiuria (2 %, 1 %)

Reproductive System and Breast Disorders: Erectile dysfunction (1 %, 1 %)

Respiratory, Thoracic and Mediastinal Disorders: Dry Throat (1 %, 1 %), oropharyngeal pain (3 %, 2 %), respiratory tract congestion (1 %, 2 %), sinus congestion (1 %, 3 %), and wheezing (1 %, 1 %)

Skin and Subcutaneous Tissue Disorders: Dermatitis (2 %, 3 %), eczema (3 %, 2 %), edema peripheral (2 %, 2 %), erythema (2 %, 3 %), rash erythematous (3 %, 1 %), and skin lesion (1 %, 1 %)

Vascular Disorders: Hypotension (1 %, 2 %)

Less Common Clinical Trial Adverse Drug Reactions (< 1 %)

Adverse reactions reported in < 1 % of patients who received the combination of VICTRELIS™ with PEGETRON® and reported at a greater rate than the PEGETRON® in SPRINT-1, SPRINT-2, and RESPOND-2 are listed.

Blood and Lymphatic System Disorders: Hemorrhagic diathesis, hemolysis, lymphadenopathy, and lymphopenia

Cardiac Disorders: Acute myocardial infarction, arrhythmia, atrial fibrillation, cardiovascular disorder, coronary artery disease, palpitations, pericardial effusion, and pericarditis

Ear and Labyrinth Disorders: Deafness, ear discomfort, and hearing impaired

Endocrine Disorders: Goiter

Eye Disorders: Abnormal sensation in eye, conjunctival hemorrhage, conjunctivitis, eye pain, eye pruritus, eye swelling, eyelid edema, increased lacrimation, ocular hyperemia, papilledema photophobia, retinal ischemia, and retinopathy

Gastrointestinal Disorders: Anal pruritus, colitis, dry lip, dysphagia, feces discolored, frequent bowel movements, gastritis, gingival bleeding, gingival pain, glossitis, lower abdominal pain, odynophagia, pancreatic insufficiency, pancreatitis, proctalgia, rectal hemorrhage, salivary hypersecretion, sensitivity of teeth, and tongue discoloration

Hepatobiliary Disorders: Cholecystitis

General Disorders and Administration Site Conditions: Chest discomfort, impaired healing, and non-cardiac chest pain

Immune System Disorders: Sarcoidosis and non-acute porphyria

Infections and Infestations Disorders: Ear infection, epiglottitis, fungal skin, infection, gastroenteritis, onychomycosis, otitis media, pharyngitis, respiratory tract infection, rhinitis, sepsis, and skin infection

Investigations: Cardiac murmur

Metabolism and Nutrition Disorders: Appetite disorder, diabetes mellitus, gout, hypercalcemia, and hypokalemia

Musculoskeletal and Connective Tissue Disorders: Arthritis, bone pain, joint swelling, muscular weakness, musculoskeletal chest pain, and musculoskeletal pain

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): Thyroid neoplasm

Nervous System Disorders: Cerebral ischemia, encephalopathy, hyperesthesia, mental impairment, neuralgia, neuropathy peripheral, and pre-syncope

Psychiatric Disorders: Abnormal behaviour, agitation, apathy, auditory hallucination, bipolar disorder, completed suicide, homicidal ideation, mental status changes, panic attack, paranoia, psychiatric decompensation, restlessness, suicide attempt, and visual hallucination

Renal and Urinary Disorders: Dysuria and nocturia

Reproductive System and Breast Disorders: Amenorrhea and aspermia

Respiratory, Thoracic and Mediastinal Disorders: Dysphonia, increased upper airway secretion, oropharyngeal blistering, orthopnea, pleural fibrosis, pleuritic pain, pulmonary embolism, and respiratory failure

Skin and Subcutaneous Tissue Disorders: Photosensitivity reaction, skin ulcer, and urticaria

Vascular Disorders: Blood pressure fluctuation, deep vein thrombosis, flushing, pallor, peripheral coldness, and venous thrombosis

Abnormal Hematologic and Clinical Chemistry Findings

Changes in selected laboratory values during treatment of adult patients with the combination of VICTRELIS™ with PEGETRON® are described in Table 3. Decreases in hemoglobin may require a decrease in dosage or interruption of RBV (see **WARNINGS AND PRECAUTIONS** and **CLINICAL TRIALS**).

Table 3: Selected Hematological Parameters

Hematological Parameters	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Patients Reporting Selected Hematological Parameters		Patients Reporting Selected Hematological Parameters	
	BOC/PegIFNα2b/RBV n=1,225 (%)	PegIFNα2b/RBV n=467 (%)	BOC/PegIFNα2b/RBV n=323 (%)	PegIFNα2b/RBV n=80 (%)
Hemoglobin (g/L)				
< 100	49	29	49	25
< 85	6	3	10	1
Platelets (x 10^9/L)				
< 50	3	1	4	0
< 25	< 1	0	0	0
Neutrophils (x 10^9/L)				
< 0.75	31	18	26	13
< 0.5	8	4	7	4

BOC = boceprevir; PegIFNα2b = peginterferon alfa-2b; RBV = ribavirin

Neutrophils and Platelets
The proportion of patients with decreased neutrophil and platelet counts was higher in the VICTRELIS™-containing arms compared to patients who received only PEGETRON®. Seven percent of patients who received the combination of VICTRELIS™ with PEGETRON® had neutrophil counts of < 0.5 x 10^9/L compared to 4 % of patients who received only PEGETRON®. Three percent of patients who received the combination of VICTRELIS™ with PEGETRON® had platelet counts of < 50 x 10^9/L compared to 1 % of patients who received only PEGETRON® (see **WARNINGS AND PRECAUTIONS**, **Hematologic, Neutropenia** and **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**).

DRUG INTERACTIONS

Serious Drug Interactions
Contraindicated Drugs: alfuzosin, amiodarone, propafenone, quinidine, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort, lovastatin, simvastatin, sildenafil or tadalafil when used for the treatment of pulmonary arterial hypertension, pimozide, drospirenone, astemizole, terfenadine, midazolam (orally administered), and triazolam (orally administered) (see **CONTRAINDICATIONS**).

Overview
Effect of Other Drugs on VICTRELIS™ Pharmacokinetics
VICTRELIS™ is partly metabolized by CYP3A4/5. Co-administration of VICTRELIS™ with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure to VICTRELIS™.

Effects of VICTRELIS™ on Pharmacokinetics of Other Drugs
VICTRELIS™ is a strong inhibitor of CYP3A4/5. Medicines metabolized primarily by CYP3A4/5 may have increased exposure when administered with VICTRELIS™, which could increase or prolong their therapeutic and adverse effects (see Table 4). VICTRELIS™ does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 *in vitro*. In addition, VICTRELIS™ does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4/5 *in vitro*.

Drug-Drug Interactions
VICTRELIS™, in combination with PegIFNα/RBV, is contraindicated when co-administered with medicines that are potent inducers of CYP3A4/5 and medicines that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events (see Table 1, **CONTRAINDICATIONS**).

Boceprevir is metabolized primarily by aldo-ketoreductase (AKR). In drug interaction trials conducted with AKR inhibitors diflunisal and ibuprofen, BOC exposure did not increase to clinically significant extent. VICTRELIS™ may be administered with AKR inhibitors. Boceprevir is partly metabolized by CYP3A4/5. *In vitro* BOC has been shown to be also a substrate of p-glycoprotein. Co-administration of VICTRELIS™ with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to BOC. Co-administration of VICTRELIS™ is contraindicated with medicines that are potent CYP3A4/5 inducers, where significantly reduced BOC plasma concentrations may be associated with reduced efficacy (see Table 1, **CONTRAINDICATIONS**).

Table 4 provides recommendations based on established, potential drug interactions or drugs contraindicated with VICTRELIS™.

Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See Tables 18 and 19)

Concomitant Drug Class/Name	Effect on Concentration of BOC or Concomitant Drug	Clinical Comment
Antiarrhythmics		
bepridil	↑ bepridil	Co-administration of VICTRELIS™ with bepridil has the potential to produce serious and/or life-threatening AEs and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with VICTRELIS™.
digoxin	↑ digoxin	Digoxin concentrations may be increased with VICTRELIS™. Use the lowest dose initially with careful titration and monitoring of serum digoxin concentrations.
Anticoagulants		
warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be altered when co-administered with VICTRELIS™. It is recommended that international normalization ratio be monitored when warfarin is co-administered with VICTRELIS™.
Antidepressants		
desipramine **trazodone**	↑ desipramine ↑ trazodone	Plasma concentrations of desipramine and trazodone may increase when administered with VICTRELIS™, resulting in AEs such as dizziness, hypotension and syncope. Use with caution and consider a lower dose of desipramine or trazodone.
Antifungals		

Concomitant Drug Class/Name	Effect on Concentration of BOC or Concomitant Drug	Clinical Comment
ketoconazole **itraconazole** **posaconazole** **voriconazole**	↑ BOC ↑ ketoconazole ↑ itraconazole ↑ posaconazole ↑ voriconazole	The results of the drug interaction study between ketoconazole (400 mg twice daily (BID)) and BOC (400 mg single dose) led to increased plasma exposure of BOC (AUC, 131 % ↑, C_{max} 41 % ↑). These changes were not considered clinically significant and no dose adjustment for BOC or ketoconazole is required. Plasma concentrations of ketoconazole, itraconazole, voriconazole or posaconazole may be increased with VICTRELIS™. When co-administration is required, doses of ketoconazole and itraconazole should not exceed 200 mg/day.
Anti-gout		
colchicine	↑ colchicine	Significant increases in colchicine levels are expected; fatal colchicine toxicity has been reported with other strong CYP3A4 inhibitors. Patients with renal or hepatic impairment should not be given colchicine with VICTRELIS™. Treatment of gout flares (during treatment with VICTRELIS™): 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. Prophylaxis of gout flares (during treatment with VICTRELIS™): If the original regimen was 0.6 mg twice a day, reduce dose to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, reduce the dose to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF) (during treatment with VICTRELIS™): Maximum daily dose of 0.6 mg (maybe given as 0.3 mg twice a day).
Anti-infective		

Concomitant Drug Class/Name	Effect on Concentration of BOC or Concomitant Drug	Clinical Comment
clarithromycin	↑ clarithromycin	Concentrations of clarithromycin may be increased with VICTRELIS™; however, no dosage adjustment is necessary for patients with normal renal function.
Antimycobacterials		
rifabutin	↓ BOC ↑ rifabutin	Increases in rifabutin exposure are anticipated, while exposure of BOC may be decreased. Doses have not been established when rifabutin is used in combination with VICTRELIS™. Concomitant use rifabutin with VICTRELIS™ is not recommended.
***Calcium Channel Blockers,* dihydropyridine**		
felodipine **nifedipine** **nicardipine**	↑ dihydropyridine calcium channel blockers	Plasma concentrations of dihydropyridine calcium channel blockers may increase when administered with VICTRELIS™. Caution is warranted and clinical monitoring is recommended.
Corticosteroid, inhaled		
budesonide **fluticasone**	↑ budesonide ↑ fluticasone	Concomitant use of inhaled budesonide or fluticasone with VICTRELIS™ may result in increased plasma concentrations of budesonide or fluticasone, resulting in significantly reduced serum cortisol concentrations. Avoid co-administration if possible, particularly for extended durations.
Corticosteroid, systemic		
dexamethasone	↓ BOC	Co-administration of VICTRELIS™ with CYP3A4/5 inducers may decrease plasma concentrations of BOC, which may result in loss of therapeutic effect. Therefore, this combination should be avoided if possible and used with caution if necessary.
Endothelin Receptor Antagonist		
bosentan	↑ bosentan	Concentrations of bosentan may be increased when co-administered with VICTRELIS™. Use with caution and monitor closely.
HCV Antivirals		

Concomitant Drug Class/Name	Effect on Concentration of BOC or Concomitant Drug	Clinical Comment
PegIFNα2b	↔ BOC ↔ PegIFNα2b	The results of the drug interaction study between PegIFNα2b (1.5 mcg/kg SC weekly) and BOC (400 mg TID) demonstrated that exposure to BOC and PegIFNα2b was not significantly affected when co-administered. No dose adjustment required for VICTRELIS™ or PegIFNα2b. The interaction between BOC and PEGIFNα2a has not been studied,
HIV-Antiviral Agents: Non-nucleoside Reverse Transcriptase Inhibitors		
efavirenz	↓ BOC ↔ efavirenz	The results of the drug interaction study between efavirenz (600 mg daily) and BOC (800 mg TID) demonstrated a decreased plasma trough concentrations of BOC (C_{min} 44 % ↓). The clinical outcome of this observed reduction of BOC trough concentrations has not been directly assessed.
HIV-Antiviral Agents: NucleosideReverse Transcriptase Inhibitors		
tenofovir	↔ BOC ↑ tenofovir	The results of the drug interaction study between tenofovir (300 mg daily) and BOC (800 mg TID) led to increased plasma exposure of tenofovir (C_{max} 32 % ↑). These changes were not considered clinically significant and no dose adjustment for VICTRELIS™ or tenofovir is required.
HIV-Antiviral Agents: HIV PIs		
ritonavir	↓ BOC ↑ or ↓ HIV PIs	The results of the drug interaction study between ritonavir (100 mg daily) and BOC (400 mg TID) demonstrated no notable change in the exposure of BOC (C_{max} 27 % ↓). These changes were not considered clinically significant and no dose adjustment for VICTRELIS™ or ritonavir is required. The effect of ritonavir-boosted HIV PIs on BOC exposure is unknown. The effect of BOC on HIV PI concentrations is unknown.
HMG-CoA Reductase Inhibitors		

Concomitant Drug Class/Name	Effect on Concentration of BOC or Concomitant Drug	Clinical Comment
atorvastatin **rosuvastatin** **pravastatin** **fluvastatin**	↑ atorvastatin ↑ rosuvastatin ↑ pravastatin ↑ fluvastatin	Increases in atorvastatin and rosuvastatin exposures are anticipated. Titrate atorvastatin dose carefully and do not exceed maximum daily dose of 20 mg during co-administration with VICTRELIS™. For rosuvastatin, pravastatin and fluvastatin, the drug interaction effect has not been studied and, therefore, caution should be used.
Immunosuppressants		
cyclosporine **sirolimus** **tacrolimus**	↑ immunosuppressants	Plasma concentrations of cyclosporine, sirolimus and tacrolimus are expected to be increased significantly during co-administration with VICTRELIS™. Close monitoring of immunosuppressant blood levels is recommended.
Inhaled beta-agonist		
salmeterol	↑ salmeterol	Concentrations of salmeterol may be increased when co-administered with VICTRELIS™. Concurrent use of inhaled salmeterol and VICTRELIS™ is not recommended due to the risk of cardiovascular events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Narcotic Analgesic/Opioid Dependence		
buprenorphine **methadone**	↑ or ↓ buprenorphine ↑ or ↓ methadone	Plasma concentrations of buprenorphine or methadone may increase or decrease when co-administered with VICTRELIS™. However, the combination has not been studied. Clinical monitoring is recommended as the dose of buprenorphine or methadone may need to be altered during concomitant treatment with VICTRELIS™.
Non-Steroidal Anti-Inflammatories (NSAIDs)		

Concomitant Drug Class/Name	Effect on Concentration of BOC or Concomitant Drug	Clinical Comment
diflunisal	↔ BOC	The results of the drug interaction study between diflunisal (250 mg BID) and BOC (800 mg TID) demonstrated no substantive change in the exposure of BOC (C_{min} 31 % ↑). These changes were not considered clinically significant and no dose adjustment for VICTRELIS™ or diflunisal is required.
ibuprofen	↔ BOC	The results of the drug interaction study between ibuprofen (600 mg TID) and BOC (400 mg single dose) demonstrated no clinically relevant change. No dose adjustment for VICTRELIS™ or ibuprofen is required.
Oral Hormonal Contraceptives		
drospirenone/ethinyl estradiol	↑ drospirenone ↓ ethinyl estradiol	The results of the drug interaction study between BOC (800 mg TID) and oral drospirenone/ethinyl estradiol (3 mg/0.02 mg daily) at steady-state demonstrated an increased systemic exposure of drospirenone (AUC, 99 %; C_{max}, 57 %) without notably affecting the exposures of ethinyl estradiol (AUC, 24 % ↓ and C_{max}, ↔). Therefore, alternative methods of non-hormonal contraception are recommended. Co-administration of VICTRELIS™ with drospirenone is contraindicated (see **CONTRAINDICATIONS**).
PDE-5 Enzyme Inhibitors		

Concomitant Drug Class/Name	Effect on Concentration of BOC or Concomitant Drug	Clinical Comment
sildenafil **tadalafil**	↑ sildenafil ↑ tadalafil	Increases in PDE-5 inhibitor concentrations are expected, and may result in an increase in AEs, including hypotension, syncope, visual disturbances, and priapism. Use of sildenafil or tadalafil when used for the treatment of PAH is contraindicated with VICTRELIS™ (see **CONTRAINDICATIONS**). <u>Use of PDE-5 inhibitors for erectile dysfunction:</u> Use with caution in combination with VICTRELIS™ with increased monitoring for PDE-5 inhibitor-associated AEs. Do not exceed the following doses: sildenafil: 25 mg every 48 hours tadalafil: 10 mg every 72 hours vardenafil: 2.5 mg every 24 hours (Dose not approved in Canada. Therefore, co-administration of vardenafil with VICTRELIS™ is not recommended)
vardenafil	↑ vardenafil	
Sedatives/Hypnotics		
alprazolam (intravenous administration) **midazolam** (intravenous administration) **triazolam** (intravenous administration)	↑ alprazolam ↑ midazolam ↑ triazolam	No interaction studies have been done with intravenous benzodiazepines. Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of VICTRELIS™ with intravenous benzodiazepines (alprazolam, midazolam, triazolam). Dose adjustment of the benzodiazepine should be considered.

Drug-Food Interactions

Increased exposure to BOC was observed following administration with food. VICTRELIS™ should be taken with food. The type of food does not affect exposure to BOC (see **ACTION AND CLINICAL PHARMACOLOGY**).

Drug-Herb Interactions

St. John's wort (*hypericum perforatum*)

Co-administration of VICTRELIS™ and St. John's wort may lead to loss of virologic response to VICTRELIS™ (see **CONTRAINDICATIONS**).

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

VICTRELIS™ should not be used as monotherapy but only in combination with PegIFNα/RBV. The Product Monographs of PegIFNα/RBV must be consulted prior to initiation of therapy with VICTRELIS™.

It is important that the dose of VICTRELIS™ (800 mg) be taken three times a day (every 7-9 hours).

Recommended Dose

The recommended dose of VICTRELIS™ is 800 mg (four 200 mg capsules) administered orally TID (every 7-9 hours) with food (a meal or light snack).

Refer to the prescribing information of PegIFNα/RBV for dosing instructions.

The following dosing recommendations differ for some subgroups from the dosing studied in the Phase 3 clinical trials (*see* **CLINICAL TRIALS***)*. Response-Guided Therapy is recommended for most individuals, but longer dosing is recommended in target groups (e.g., patients with cirrhosis).

Patients without Cirrhosis Who Are Previously Untreated or Who Are Previous Partial Responders or Relapsers to PegIFNα/RBV Therapy

- Initiate therapy with PegIFNα/RBV for 4 weeks (TWs 1-4).
- Add VICTRELIS™ 800 mg (four 200 mg capsules) orally TID (every 7-9 hours) to PegIFNα/RBV regimen at TW 5. Based on whether patients are previously untreated or previous treatment failures and their HCV-RNA levels at TW 8, TW 12 and TW 24, use the following RGT guidelines to determine duration of treatment (see Table 5).

Table 5: Duration of Therapy using RGT Guidelines in Patients without Cirrhosis who are Previously Untreated and Patients who are Previous Treatment Failures (previous partial responders and relapsers)[a]

	ASSESSMENT[b] (HCV-RNA Results[c])		ACTION
	At TW 8	At TW 24	
Previously Untreated Patients	Undetectable	Undetectable	Stop three-medicine regimen (PegIFNα/RBV and BOC) at TW 28. Treatment is completed.
	Detectable	Undetectable	1. Continue all three medicines until TW 28, and then 2. Administer PegIFNα/RBV until TW 48.
Previous Treatment Failures (previous partial responders and relapsers)	Undetectable	Undetectable	Stop three-medicine regimen at TW 36. Treatment is completed.
	Detectable	Undetectable	1. Continue all three medicines until TW 36, and then 2. Administer PegIFNα/RBV until TW 48.

a: Previous Treatment Failures to PegIFNα/RBV Therapy: Previous Partial responders (Patients with a decrease in HCV-RNA viral load ≥ 2-$\log_{10}$ by Week 12 but never achieved SVR); Relapsers (Patients with undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma).

b: **Treatment Futility: If the patient has HCV-RNA results ≥ 100 IU/mL at TW 12 or if the patient has confirmed detectable HCV-RNA at TW 24, then discontinue the three-medicine regimen.**

c: In clinical trials, plasma HCV-RNA was measured using a Roche COBAS* TaqMan* assay with a lower limit of detection of 9.3 IU/mL and a lower limit of quantification of 25 IU/mL (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Response-Guided Therapy is not recommended for patients with prior null response or patients with cirrhosis.

Patients with Prior Null Response
Response-Guided Therapy was not studied in subjects who had less than a 2-$\log_{10}$ HCV-RNA decline by TW 12 during prior therapy with PegIFNα/RBV. If considered for treatment, these subjects should receive 4 weeks of PegIFNα/RBV followed by 44 weeks of VICTRELIS™ 800 mg (four 200 capsules) orally TID (every 7-9 hours) in combination with PegIFNα/RBV (see **CLINICAL TRIALS**).

Patients without Cirrhosis who are Previously Untreated with a Poor Interferon Response
In addition, consideration should be given to treating Previously Untreated patients who are poorly interferon responsive (less than a 1.0-$\log_{10}$ decline in HCV-RNA at TW 4 with PegIFNα/RBV alone) with 4 weeks PegIFNα/RBV followed by 44 weeks of VICTRELIS™ 800 mg (four 200 mg capsules) TID (every 7-9 hours) in combination with PegIFNα/RBV (see **CLINICAL TRIALS**).

Patients with Cirrhosis
Patients with compensated cirrhosis should receive 4 weeks PegIFNα/RBV followed by 44 weeks VICTRELIS™ 800 mg (four 200 capsules) orally TID (every 7-9 hours) in combination with PegIFNα/RBV.

Dosage Adjustment
Dose reduction of VICTRELIS™ is not recommended.

VICTRELIS™ **must not** be administered in the absence of PegIFNα/RBV.

If a patient has a serious adverse reaction potentially related to PegIFNα and/or RBV, the PegIFNα and/or RBV dose should be reduced or discontinued. Refer to the Product Monographs for PegIFNα/RBV for additional information about how to reduce and/or discontinue the PegIFNα and/or RBV dose.

Renal Impairment
No dose adjustment of VICTRELIS™ is required in patients with any degree of renal impairment (see **DETAILED PHARMACOLOGY**).

Hepatic Impairment
No dose adjustment of VICTRELIS™ is required for patients with mild, moderate or severe hepatic impairment (see **DETAILED PHARMACOLOGY, Pharmacokinetics**, **Special Populations and Conditions**, Hepatic Insufficiency). Safety and efficacy of VICTRELIS™ have not been studied in patients with decompensated cirrhosis. See Product Monographs for PegIFNα/RBV for contraindication in hepatic decompensation.

Discontinuation of Dosing Based on Treatment Futility
Discontinuation of therapy is recommended in all patients with:
1) HCV-RNA levels ≥ 100 IU/mL at TW 12; or
2) Confirmed detectable HCV-RNA levels at TW 24.

Missed Dose
If a patient misses a dose and it is less than 2 hours before the next dose is due, the missed dose should be skipped.

If patient misses a dose and it is 2 or more hours before the next dose is due, the patient should take the missed dose with food and resume the normal dosing schedule.

Administration
Take orally with food (a meal or light snack).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Daily doses of 3,600 mg have been taken by healthy volunteers for 5 days without untoward symptomatic effects.

There is no specific antidote for overdose with VICTRELIS™. Treatment of overdose with VICTRELIS™ should consist of general supportive measures, including monitoring of vital signs, and observation of the patient's clinical status. VICTRELIS™ is not eliminated by dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Description
Boceprevir is manufactured as an approximately equal mixture of two diastereoisomers; the pharmacologically active SCH 534128 (S-isomer) and SCH 534129 (R-isomer).

Mechanism of Action
VICTRELIS™ is an inhibitor of the HCV NS3/4A protease. VICTRELIS™ covalently, yet reversibly, binds to the NS3/4A protease active site serine (Ser139) through a (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells.

Pharmacodynamics

Evaluation of Effect of VICTRELIS™ on QTc Interval

In a randomized, multiple-dose, placebo and active controlled four-way cross-over study, BOC was evaluated for the effect on QT/QTc intervals at the 800 mg TID (therapeutic dose) and the 1,200 mg TID dose in 36 healthy subjects after multiple dosing for 5 days. The mean maximum concentrations at the 800 and 1,200 mg doses were 1,690 ng/mL and 1,940 ng/mL, respectively.

There was no significant difference in the QTc interval between BOC and placebo. At the mean maximum BOC exposures of 1,690 and 1,940 ng/mL, which were achieved at 2 hours postdose for the 800 and 1,200 mg doses, the mean increases in placebo-adjusted QTcF were 4.5 and 0.3 ms with the upper limits of the 95 % CI of 7.3 and 3.1 ms, respectively. The maximum observed mean increases in placebo-adjusted QTcF occurred at 4 hours post-dose, and were 5.8 and 2.9 ms with the upper limits of the 95 % CI of 8.7 and 5.7 ms, respectively. Therefore, in this study with demonstrated ability to detect small effects, the upper bound of the one-sided 95 % confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on individual correction method was below 10 ms, the threshold for regulatory concern. The dose of 1,200 mg yields a BOC maximum exposure increase of approximately 15 % which may not cover exposures due to co-administration with strong CYP3A4 inhibitors or use in patients with severe hepatic impairment. However, at the doses studied in the thorough QT study, no apparent concentration-QT relationship was identified. Thus, there is no expectation of a QTc effect under a higher exposure scenario.

Pharmacokinetics

General Pharmacokinetic Characteristics

VICTRELIS™ capsules contain an approximately equal mixture of two diastereoisomers. In the plasma the diastereoisomer ratio is about 2:1 in favour of the active diastereoisomer, SCH 534128. The plasma concentrations of BOC described below consist of both diastereoisomers. The PK properties of BOC have been evaluated in healthy adult subjects and HCV-infected patients (see Table 6 below and Table 16, **DETAILED PHARMACOLOGY**, **Pharmacokinetics**).

Table 6: Summary of boceprevir's PK Parameters at Steady-State in Healthy Subjects (n = 71)

Dose (mg)	C_{max} (ng/mL)	$t_{½}$ (h)	$AUC_{(\tau)}$ (ng·h/mL)	Clearance (L/h)	Volume of Distribution (L)
800 TID	1,723	3.0	5,408	159	717

$AUC_{(\tau)}$ = area under the plasma concentration–time curve from time 0 dosing interval

The PK profiles of single and multiple doses of BOC from 50 mg up to 800 mg, and 100 mg up to 1,200 mg, respectively, have been evaluated. In general, the PK results were similar between healthy and HCV subjects.

Absorption

Boceprevir was absorbed following oral administration with a median T_{max} of 2 hours. Steady state AUC, C_{max} and C_{min} increased in a less-than dose-proportional manner and individual exposures overlapped substantially at 800 mg and 1,200 mg, suggesting diminished absorption at higher doses. Accumulation is minimal and PK steady state is achieved after approximately 1 day of TID dosing.

The absolute bioavailability of VICTRELIS™ has not been studied.

Effects of Food on Oral Absorption
VICTRELIS™ should be administered with food. Food enhanced the exposure of BOC by up to 60 % at the 800 mg TID dose when administered with a meal, relative to the fasting state. The bioavailability of BOC was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. Therefore, VICTRELIS™ may be taken without regard to either meal type or timing.

Distribution
Boceprevir has a mean apparent volume of distribution (Vd/F) of approximately 717 L (n = 71) at steady state. Human plasma protein binding is approximately 75 % following a single dose of VICTRELIS™ 800 mg. Boceprevir is administered as an approximately equal mixture of two diastereomers which rapidly interconvert in plasma: one diastereomer is pharmacologically active and the other diastereomer is inactive.

Metabolism
Studies *in vitro* indicate that BOC primarily undergoes metabolism through the AKR-mediated pathway to ketone-reduced metabolites that are inactive against HCV. After a single 800 mg oral dose of ^{14}C-BOC, the most abundant circulating metabolites were a diasteriomeric mixture of ketone-reduced metabolites with a mean exposure approximately 4–fold greater than that of BOC. Boceprevir also undergoes, to a lesser extent, oxidative metabolism mediated by CYP3A4/5.

Excretion
Boceprevir is eliminated with a mean plasma half-life ($t_{½}$) of approximately 3.0 hours (n = 71). Boceprevir has a mean total body clearance (CL/F) of approximately 159 L/h (n = 71). Following a single 800 mg oral dose of ^{14}C-BOC, approximately 79 % and 9 % of the dose was excreted in feces and urine, respectively, with approximately 8 % and 3 % of the dosed radiocarbon eliminated as BOC in feces and urine. The data indicate that BOC is eliminated primarily by the liver.

Special Populations and Conditions

Pediatrics
The safety, efficacy, and PK profile of VICTRELIS™ in pediatric patients below the age of 18 years have not been established.

Geriatrics
Population PK analysis of VICTRELIS™ indicated that age had no apparent effect on exposure.

Gender
No gender-related PK differences have been observed in adult patients.

Race
Population PK analysis of VICTRELIS™ indicated that race had no apparent effect on exposure.

Hepatic Insufficiency
In a study of patients with varying degrees of stable chronic liver impairment (mild, moderate and severe), no clinically significant differences in PK parameters were found and no dosage adjustment is recommended (see **DETAILED PHARMACOLOGY, Pharmacokinetics**, **Special Populations and Conditions**, Hepatic Insufficiency). See PegIFNα/RBV Product Monograph for contraindication in patients with hepatic decompensation.

Renal Insufficiency
No clinically significant differences in PK parameters were observed between patients with End-Stage Renal Disease (ESRD) and healthy subjects (see **DETAILED PHARMACOLOGY, Pharmacokinetics**, **Special Populations and Conditions**, Renal Insufficiency). No dosage adjustment is required in these patients and in patients with any degree of renal impairment.

STORAGE AND STABILITY
VICTRELIS™ Capsules should be refrigerated at 2°C – 8°C until dispensed to the patient.

For patient use, the product may be stored in the refrigerator until the expiration date printed on the label. The product can also be stored at room temperature (15°C – 30°C) for up to 3 months. Store in the original container.

SPECIAL HANDLING INSTRUCTIONS
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING
Dosage Form
VICTRELIS™ 200 mg capsules are available as hard gelatin capsules for oral administration.

Composition
Each capsule has a yellowish-brown, opaque cap with the Merck logo imprinted in red ink and off-white, opaque body with the code "314" imprinted in red ink.

Each VICTRELIS™ capsule contains 200 mg of BOC and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pre-gelatinized starch, and sodium lauryl sulfate. The capsule shell consists of gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The capsule is printed with red ink. The red ink contains red iron oxide and shellac.

Packaging
Peelable aclar/PVC/aluminium blisters containing 12 capsules.

7 blisters per folding carton and 2 folding cartons per outer carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:

boceprevir

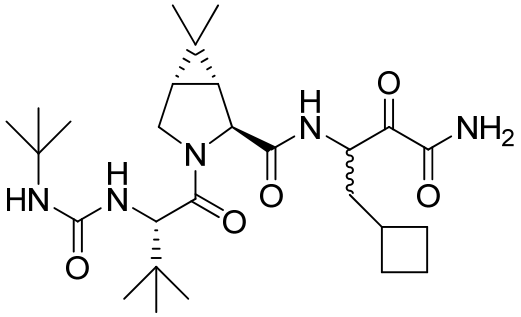
Chemical name:

(1R,5S)-N-[3-Amino-1- (cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide

Molecular formula and molecular mass:

$C_{27}H_{45}N_5O_5$ 519.7

Structural formula:



Physicochemical properties:

Appearance: Boceprevir is a white to off-white amorphous powder.

Solubility: Boceprevir is freely soluble in methanol, ethanol and isopropanol and slightly soluble in water (1.5 mg/mL at 25°C).

CLINICAL TRIALS

The efficacy of BOC as a treatment for CHC (genotype 1) infection was assessed in approximately 1,500 adult patients who were previously untreated (SPRINT-2) or who had failed previous therapy (RESPOND-2) in Phase 3 clinical studies.

Previously Untreated Patients (SPRINT-2)

Demographic, Disease Characteristics and Trial Design

SPRINT-2 (P05216) was conducted in previously untreated HCV, genotype 1-infected patients. A summary of the clinical trial design and patient demographics are shown in Table 7. Patients were randomized in a 1:1:1 ratio in two cohorts (Cohort 1/non-Black and Cohort 2/Black) and stratified by HCV genotype (1a or 1b) and by HCV-RNA viral load (≤ 400,000 IU/mL vs > 400,000 IU/mL).

Table 7: Study P05216 (SPRINT-2) - Summary of Trial Design for Cohort 1 + 2 (all patients)

Trial Design	Dosage and Route of Administration	Treatment Regimen[a]	Total Duration (weeks)	No. of Patients	Gender M/F Race W/B/O Mean Age (years) (Range)
Phase 3, randomized, double-blinded, placebo-controlled, multi-centre	BOC - 800 mg TID, PO PegIFNα2b - 1.5 mcg/kg/week, SC RBV - 600 to 1,400 mg/day BID (weight based dosing), PO	Control PegIFNα2b/RBV-4 lead-in + (Pbo/ PegIFNα2b/RBV-44)	Pbo - 44 PegIFNα2b/RBV - 48	363	206/157 296/52/15 48.6 (18-75)
		RGT PegIFNα2b/RBV-4 lead-in + (BOC/ PegIFNα2b/RBV-24)[b] OR (BOC+ PegIFNα2b/RBV-24/ PegIFNα2b/RBV-20)[c]	BOC - 24 PegIFNα2b/RBV - 28 OR BOC -24 PegIFNα2b/RBV - 48	368	229/139 304/52/12 49.8 (21-76)
		Not RGT PegIFNα2b/RBV-4 lead-in + (BOC/ PegIFNα2b/RBV-44)	BOC - 44 PegIFNα2b/RBV - 48	366	221/145 295/55/16 48.9 (21-67)

BOC = Boceprevir; PegIFNα2b = peginterferon alfa-2b; RBV = ribavirin; Pbo = Placebo
TID = three times daily; BID = twice daily; PO = orally; SC = subcutaneous
RGT = Response-Guided Therapy (based on TW 8 results)
Race W/B/O = White/Black/Other
a: The number indicates the number of weeks of treatment
b: Early responders (Undetectable HCV-RNA at TW 8 through TW 24)
c: Late responders (Detectable HCV-RNA at TW 8 or after and undetectable at TW 24)
Futility Rule: All patients with detectable HCV-RNA in plasma at TW 24 were discontinued from treatment.

Table 8: Baseline Characteristics of Previously Untreated Patients with Chronic Hepatitis C Genotype 1 (SPRINT-2) in Cohort 1 plus Cohort 2 (all patients)

	BOC/Pegα2b/RBV (RGT) n = 368	BOC/Pegα2b/RBV-48 n = 366	Pegα2b/RBV-48 n = 363
Mean Plasma HCV-RNA (Log_{10} copies/mL)	6.52	6.53	6.54
Viral Load (IU/mL)			
≤ 400,000	9 %	7 %	7 %
> 400,000	91 %	93 %	93 %
HCV Subtype (Trugene)[a]			
1 (subtype unknown)	15 %	13 %	17 %
1a	49%	51 %	49 %
1b	36 %	36 %	35 %
METAVIR Fibrosis Score[b]			
F0/1/2	87 %	86 %	90 %
F3/4	9 %	11 %	7 %
Missing	4 %	3 %	3 %
Baseline Platelet Count (10^9/L) %			
< 150	9 %	10 %	7 %
≥ 150	91 %	90 %	93 %
Baseline ALT, %			
Normal	20 %	23 %	26 %
Elevated	80 %	77 %	74 %
Baseline Steatosis[c] %			
0/1/2	94 %	97 %	96%
3	2 %	1 %	1 %
Missing	4 %	3 %	3 %

a: HCV subtype as determined by TRUGENE HCV 5NC assay was used in subject stratification.
b: Liver histology based on central pathologist's reading. F0=no fibrosis, F1=portal fibrosis without septa, F2=few septa, F3=numerous septa without cirrhosis (bridging fibrosis), F4=cirrhosis (advanced fibrosis)
c: Liver histology based on central pathologist's reading of the percentage cells that contain lipids. Score 0 = 0 %, score 1 = > 0 % and ≤ 5 %, score 2 = > 5 % and ≤ 32 %, score 3 = > 32 % and ≤ 66 %.

Two percent of previously untreated patients used statins or were on opioid substitution therapy.

Study Results

The addition of BOC to PegIFNα2b/RBV significantly increased the SVR rates compared to PegIFNα2b/RBV alone in the combined cohort (63 % to 66 % BOC-containing arms vs. 38 % PegIFNα2b/RBV-48 control) for randomized patients who received at least one dose of any study medication (Full-Analysis-Set population) and decreased the length of therapy to 28 weeks for early responders (see Table 9). Overall, these SVR rates were approximately two-fold higher in patients who received the combination of BOC with PegIFNα2b/RBV compared to the control group. Sustained Virologic Response rates for Blacks who received the combination of BOC with PegIFNα2b/RBV were 42 % to 53 %; these rates are approximately two-fold higher than the SVR rate for the PegIFNα2b/RBV-48 control (23 %) (see Table 9). A secondary analysis of subjects who received at least one dose of BOC or placebo after the four-week lead-in with PegIFNα2b/RBV (Modified-Intent-to-Treat population) demonstrated SVR rates in the combined cohort of 67 % to 68 % BOC-containing arms vs. 40 % PegIFNα2b/RBV-48 control.

Table 9: Sustained Virologic Response, End of Treatment, Relapse[a] and Discontinuation Rates in Previously Untreated Patients (SPRINT-2)

	FAS[b]		
	BOC/PegIFNα2b/ RBV (RGT)	**BOC/PegIFNα2b/ RBV-48**	**PegIFNα2b/RBV-48 (Control)**
Cohort 1 Plus Cohort 2 (All Patients)	**n = 368**	**n = 366**	**n = 363**
SVR[c] P value[d] ΔSVR 95 % CI for Δ SVR	63.3 % < 0.0001 25.6 (18.6, 32.6)	66.1 % < 0.0001 28.4 (21.4, 35.3)	37.7 %
EOT[e] (Undetectable HCV-RNA)	70.9 %	75.7 %	52.6 %
Relapse	9.3 %	9.1 %	22.2 %
Discontinuation During Lead-in Period After addition of BOC/placebo Discontinuation due to AEs after addition of BOC/placebo	 5 % 35 % 10 %	 3 % 39 % 14 %	 5 % 54 % 12 %
Treatment Failure after addition of BOC/placebo	16 %	13 %	34 %
Completed Treatment	62 %	59 %	44 %
Completed Follow-up	98 %	98 %	86 %
Deaths	< 1 %	< 1 %	1 %
Cohort 1 (Non-Black)	**n = 316**	**n = 311**	**n = 311**
SVR[c] P value[d] ΔSVR 95 % CI for Δ SVR	66.8 % < 0.0001 26.6 (19.1, 34.1)	68.5 % < 0.0001 28.3 (20.8, 35.8)	40.2 %
EOT[e] (Undetectable HCV-RNA)	74.4 %	77.5 %	56.6 %
Relapse	9.1 %	7.8 %	22.8 %
Discontinuation During Lead-in Period After addition of BOC/placebo Discontinuation due to AEs after addition of BOC/placebo	 4 % 32 % 10 %	 4 % 36 % 14 %	 5 % 50 % 12 %
Treatment Failure after addition of BOC/placebo	14 %	11 %	31 %
Completed Treatment	65 %	61 %	48 %
Completed Follow-up	97 %	98 %	86 %
Deaths	< 1 %	< 1 %	1 %
Cohort 2 (Black)	**n = 52**	**n = 55**	**n = 52**
SVR[c] P value[d] ΔSVR 95 % CI for Δ SVR	42.3 % 0.0440 19.2 (1.6, 36.9)	52.7 % 0.0035 29.7 (12.2, 47.1)	23.1 %
EOT[e] (Undetectable HCV-RNA)	50.0 %	65.5 %	28.8 %
Relapse	12.0 %	17.1 %	14.3 %
Discontinuation During Lead-in Period After addition of BOC/placebo Discontinuation due to AEs after addition of BOC/placebo	 10 % 49 % 13 %	 0 % 55 % 16 %	 10 % 77 % 15 %
Treatment Failure after addition of BOC/placebo	28 %	25 %	53 %
Completed Treatment	46 %	45 %	21 %
Completed Follow-up	100 %	98 %	86 %
Deaths	0 %	0 %	0 %

a: Relapse rate was the proportion of patients with undetectable HCV-RNA at End of Treatment (EOT) and detectable HCV-RNA at End of Follow-up (EOF) among patients who were undetectable at EOT and not missing EOF data.

b: The Full-Analysis Set (FAS) consisted of all randomized patients (n=1,097) who received at least one dose of any study medication (PegIFNα2b, RBV, or BOC).

c: SVR: The last available value in the period at or after FW 24. If there is no such value, the FW 12 value is carried forward.

d: Using the Cochran-Mantel Haenzel Chi-square test adjusted for baseline stratification factors: viral load (> 400,000 vs. < = 400,000 IU/mL) and Genotype (1a vs. 1b).

e: Responders at the End of Treatment.

Sustained Virologic Response Based on Lead-in Response

During the clinical studies, the lead-in phase during which PegIFNα2b/RBV was administered for four weeks allowed for the assessment of patient interferon responsiveness immediately before the addition of BOC.

Interferon-responsiveness (as defined by ≥ 1-$\log_{10}$ decline in viral load at TW 4) was predictive of SVR. Boceprevir-treated patients who demonstrated interferon responsiveness by TW 4 achieved SVR rates of 81 % (203/252) in BOC-RGT arm and 79% (200/254) in BOC-PR48 arm, compared to 52 % (134/260) in patients treated with standard of care. Boceprevir-treated patients with < 1-$\log_{10}$ decline in viral load at TW 4 (poor interferon-responsiveness) achieved SVR rates of 28 % (27/97) in BOC-RGT arm and 38% (36/95) in BOC-PR48 arm compared to 4 % (3/83) in patients treated with standard of care.

Sustained Virologic Response Based on TW 8 HCV-RNA Results

Response-Guided Therapy based on TW 8 response is equally effective as adding BOC to the 48-week standard of care regimen. Fifty-seven percent (208/368) of patients in the BOC-RGT arm had undetectable HCV-RNA at TW 8 (early responders). After accounting for treatment discontinuations, 44 % (162/368) of patients reached TW 24 and were assigned a short (28 weeks) treatment with BOC in combination with PegIFNα2b/RBV in the BOC-RGT arm. These BOC-RGT early responders demonstrated similar SVR rates (156/162 or 96 %) after 28 weeks of treatment compared with the matched population in the BOC/PegIFNα2b/RBV-48 arm (e.g., those patients in the BOC/PegIFNα2b/RBV-48 arm who also had undetectable HCV-RNA at TW 8 through TW 24) (155/161 or 96 %) (see Table 10).

Table 10: Sustained Virologic Response, End of Treatment and Relapse Rates in Experimental Arms with Undetectable or Detectable HCV-RNA at TW 8 through TW 24 in Previously Untreated Patients in the Combined Cohort

	FAS[a]			
	Undetectable HCV-RNA at TW 8[b] (Early Responders)		Detectable HCV-RNA at TW 8[b] (Late Responders)	
	BOC-RGT[c]	BOC/PegIFNα2b/RBV-48	BOC-RGT[c]	BOC/PegIFNα2b/RBV-48
SVR[d] % (n/N)	96 (156/162)	96 (155/161)	72 (59/82)	75 (55/73)
EOT (Undetectable HCV-RNA) % (n/N)	100 (162/162)	99 (159/161)	80 (66/82)	90 (66/73)
Relapse[e] % (n/N)	3 (5/161)	1 (2/157)	11 (7/66)	14 (9/64)

a: The Full-Analysis Set (FAS) consisted of all randomized patients (n = 1,097) who received at least one dose of any study medication (PegIFNα2b, RBV, or BOC).

b: Per the study design, patients with undetectable HCV-RNA at TW 8 and all subsequent assays through TW 24 ended treatment at TW 28 (treatment duration assigned by Interactive Voice Response System (IVRS).

c: boceprevir-RGT – Patients received PegIFNα2b/RBV for 4 weeks, then BOC 800 mg TID + PegIFNα2b/RBV as follows: BOC 800 mg TID + PegIFNα2b/RBV for 24 weeks (patients with undetectable HCV-RNA at TW 8 (early responders) and all subsequent assays through TW 24) or BOC 800 mg TID + PegIFNα2b/RBV for 24 weeks followed by placebo + PegIFNα2b/RBV for 20 weeks (patients with detectable HCV-RNA at TW 8 up to TW 24; but achieving undetectable HCV-RNA at TW 24).

d: Sustained Virologic Response: The last available value in the period at and after FW 24. If there is no such value, the FW 12 value was carried forward.

e: Relapse rate was the proportion of patients with undetectable HCV-RNA at EOT and detectable HCV-RNA at EOF among patients who were undetectable at EOT and not missing EOF data.

Similarly, subjects in the BOC-RGT arm with detectable HCV-RNA at any assay from TW 8 up to TW 24, but achieving undetectable HCV-RNA at TW 24 (82/368, 22 %), were considered late responders and received an initial 4 weeks of PegIFNα2b/RBV, then 24 weeks of BOC with PegIFNα2b/RBV followed by 20 weeks of PegIFNα2b/RBV alone in the BOC-RGT arm. These BOC-RGT late responders who were assigned to the BOC-RGT arm that received 48 weeks of treatment also had SVR rates (72 %, 59/82) that were similar to those in the matched subjects in the BOC/PegIFNα2b/RBV-48 arm (75 %, 55/73) (see Table 10). These data support the concept that continued therapy with BOC in addition to PegIFNα2b/RBV standard of care after TW 28 (as executed in the BOC/PegIFNα2b/RBV-48 arm) does not improve SVR rates in late responders who receive a total of 48 weeks of PegIFNα2b/RBV treatment.

Sustained Virologic Response Based on Baseline Factors

Sustained Virologic Response rates in patients in the BOC-RGT and BOC/PegIFNα2b/RBV-48 compared to patients who received PegIFNα2b/RBV alone with the following baseline factors were as follows: Baseline HCV-RNA > 400,000 IU/mL (62 % (208/336) and 65 % (220/341) vs. 34 % (116/337)), advanced liver disease (F3/4) (41 % (14/34) and 52 % (22/42) vs. 38 % (9/24)), cirrhotics (F4) (31% (5/16) and 42% (10/24) vs. 46% (6/13)), genotype 1a (59 % (139/234) and 62 % (147/237) vs. 34 % (78/227)), and genotype 1b (71 % (88/124) and 73 % (85/117) vs. 40 % (48/121)).

Among previously untreated patients with advanced liver disease (F3/4), the SVR rate was higher in patients who received four weeks of therapy with PegIFNα2b/RBV followed by 44 weeks of BOC/PegIFNα2b/RBV (52 %) than in patients who received BOC-RGT (41 %). However, these conclusions were based on a small sample size of patients with advanced fibrosis.

Previous Treatment Failures (RESPOND-2)

Demographic, Disease Characteristics and Trial Design

RESPOND-2 (P05101) was conducted in previously treated HCV, genotype 1-infected patients. A summary of the clinical trial design and patient demographics are shown in Table 11. Patients were randomized in a 1:2:2 ratio and stratified based on response to their previous qualifying regimen (relapsers vs. non-responders) and by HCV subtype (1a vs. 1b).

Table 11: Study P05101 (RESPOND-2) - Summary of Trial Design

Trial Design	Dosage and Route of Administration	Treatment Regimen[a]	Total Duration (weeks)	No. of Patients	Gender M/F Race W/B/O Mean Age (years) (Range)
Phase 3, randomized, double-blinded, placebo-controlled, multi-centre	BOC - 800 mg TID, PO PegIFNα2b - 1.5 mcg/kg/week, SC RBV - 600 to 1,400 mg/day BID (weight based dosing), PO	Control PegIFNα2b/RBV-4 lead-in + (Pbo/ PegIFNα2b/RBV-44)	Pbo - 44 PegIFNα2b/RBV - 48	80	58/22 67/12/1 52.9 (29-70)
		RGT PegIFNα2b/RBV-4 lead-in + (BOC/ PegIFNα2b/RBV-32)[b] OR (BOC+ PegIFNα2b/RBV-32/ PegIFNα2b/RBV-12)[c]	BOC - 24 PegIFNα2b/RBV - 36 OR BOC -24 PegIFNα2b/RBV - 48	162	98/64 142/18/2 52.9 (29-74)
		Not RGT PegIFNα2b/RBV-4 lead-in + (BOC/ PegIFNα2b/RBV-44)	BOC - 44 PegIFNα2b/RBV - 48	161	112/49 135/19/7 52.3 (26-74)

BOC = boceprevir; PegIFNα2b = peginterferon alfa-2b; RBV = ribavirin; Pbo = Placebo
TID = three times daily; BID = twice daily; PO = orally; SC = subcutaneous
RGT = Response-Guided therapy (based on TW 8 results)
Race W/B/O = White/Black/Other
a: The number indicates the number of weeks of treatment
b: Early responders (Undetectable HCV-RNA at TW 8)
c: Late responders (Detectable HCV-RNA at TW 8 but subsequently undetectable at TW 12)
Futility Rule: All patients with detectable HCV-RNA in plasma at TW 12 were discontinued from treatment.

Table 12: Baseline Characteristics of Previous Treatment Failures with Chronic Hepatitis C Genotype 1 (RESPOND-2)

	BOC/PegIFNα2b/RBV (RGT) n = 162	BOC/PegIFNα2b/RBV-48 n = 161	PegIFNα2b/RBV-48 n = 80
Mean Plasma HCV-RNA (Log_{10} copies/mL)	6.63	6.69	6.52
Viral Load (IU/mL)			
≤ 400,000	4 %	4 %	8 %
> 400,000	96 %	96 %	92 %
HCV Subtype (Trugene)[a]			
1 (subtype unknown)	8 %	11 %	8 %
1a	46 %	48 %	48 %
1b	46 %	42 %	45 %
METAVIR Fibrosis Score[b]			
F0/1/2	74 %	72 %	76 %
F3/4	19 %	20 %	19 %
Missing	7 %	8 %	5 %
Response to Qualifying Regimen			
Nonresponder	35 %	36 %	36 %
Relapser	65 %	64 %	64 %
Baseline Platelet Count (10^9/L) %			
< 150,000	13 %	12 %	13 %
≥ 150,000	87 %	88 %	88 %
Baseline ALT, %			
Normal	33 %	29 %	31 %
Elevated	67 %	71 %	69 %
PegIFNα used in Qualifying Regimen			
PEGα2a	49 %	42 %	53 %
PEGα2b	51 %	58 %	48 %
Baseline Steatosis[c] %			
0/1/2	87 %	93 %	93 %
3	4 %	1 %	1 %
4	0 %	0 %	1 %
Missing	8 %	7 %	5 %

a: HCV subtype as determined by TRUGENE HCV 5NC assay was used in subject stratification.

b: Liver histology based on central pathologist's reading. F0=no fibrosis, F1=portal fibrosis without septa, F2=few septa, F3=numerous septa without cirrhosis (bridging fibrosis), F4=cirrhosis (advanced fibrosis)

c: Liver histology based on central pathologist's reading of the percentage cells that contain lipids. Score 0=0 %, score 1= > 0 % and ≤5 %, score 2 = > 5 % and ≤32 %, score 3 = > 32 % and ≤66 %, score 4 = > 66 %.

Three percent of patients who failed previous therapy used statins, and one percent was on opioid substitution therapy.

Study Results

The addition of BOC to the PegIFNα2b/RBV therapy significantly increased the SVR rates compared to PegIFNα2b/RBV therapy alone (59 % to 66 % BOC-containing arms vs. 21 % PegIFNα2b/RBV-48 control) for randomized patients who received at least one dose of any study medication (Full-Analysis Set population) and decreased the length of therapy to 36 weeks for many previous treatment failures (see Table 13). Overall, these SVR rates were approximately three-fold higher in patients who received the combination of BOC with PegIFNα2b/RBV compared to the control group. A secondary analysis of subjects who received at least one dose of BOC or placebo after the four week lead-in with PegIFNα2b/RBV (Modified Intent to Treat population) demonstrated SVR rates of 61 % to 67 % in the BOC-containing arms compared to 22 % PegIFNα2b/RBV-48 control.

Table 13: Sustained Virologic Response, End of Treatment, and Relapse[a] Rates for Previous Treatment Failures

	FAS[b]		
	BOC/PegIFNα2b/RBV (RGT) n =162	**BOC/PegIFNα2b/RBV -48 n = 161**	**PegIFNα2b/RBV-48 (Control) n = 80**
SVR[c] P value[d] ΔSVR 95 % CI for Δ SVR	58.6 % < 0.0001 37.4 (25.7, 49.1)	66.5 % < 0.0001 45.2 (33.7, 56.8)	21.3 %
EOT (Undetectable HCV-RNA)	70.4 %	77.0 %	31.3 %
Relapse	15.3 %	11.6 %	32.0 %
Discontinuation During Lead-in Period After addition of BOC/placebo Discontinuation due to AEs after addition of BOC/placebo	 4 % 33 % 6 %	 1 % 34 % 12 %	 3 % 71 % 1 %
Treatment Failure after addition of BOC/placebo	23 %	18 %	63 %
Completed Treatment	64 %	65 %	29 %
Completed Follow-up	97 %	96 %	97 %
Deaths	< 1 %	0	0

a: Relapse rate was the proportion of patients with undetectable HCV-RNA at EOT and detectable HCV-RNA at EOF among patients who were undetectable at EOT and not missing EOF data

b: The FAS consisted of all randomized patients (n=403) who received at least one dose of any study medication (PegIFNα2b, RBV, or BOC).

c: Sustained Virologic Response: The last available value in the period at and after FW 24. If there is no such value, the FW 12 value was carried forward.

d: Using the Cochran-Mantel Haenzel Chi-square test adjusted for the baseline stratification factors: prior response status (some negative vs. never negative) and Genotype (1a vs. 1b).

<u>Sustained Virologic Response Based on Previous Treatment Response and Lead-in Response</u>

Achievement of SVR was associated with the patient's response to PegIFNα2b/RBV therapy, whether defined by classification of response to previous treatment, or by a decrease in HCV-RNA at TW 4 (see Table 14). The TW 4 response was a stronger predictor of SVR compared to response to previous treatment and allowed the determination of the patient's on-treatment interferon responsiveness.

Table 14: Sustained Virologic Response, End of Treatment, Relapse[a] Rates for Previous Treatment Failures by Previous Treatment Response and Lead-In Response (FAS[b])

	Previous Treatment Response		Lead-In Response[e] (TW 4) HCV-RNA Log Reduction	
	Previous Non-Responders[c]	Previous Relapsers[d]	< 1-$\log_{10}$ decline	≥ 1-$\log_{10}$ decline
PegIFNα2b/RBV-48 (n = 80)				
SVR[f] % (n/N)	7 (2/29)	29 (15/51)	0 (0/12)	25 (17/67)
Relapse[a] % (n/N)	33 (1/3)	32 (7/22)	0 (0/0)	32 (8/25)
EOT % (n/N)	10 (3/29)	43 (22/51)	0 (0/12)	37 (25/67)
BOC-RGT (n = 162)				
SVR[f] % (n/N)	40 (23/57)	69 (72/105)	33 (15/46)	73 (80/110)
Relapse[a] % (n/N)	18 (5/28)	14 (12/83)	12 (2/17)	16 (15/94)
EOT % (n/N)	54 (31/57)	79 (83/105)	41 (19/46)	86 (95/110)
BOC/PegIFNα2b/RBV-48 (n = 161)				
SVR[f] % (n/N)	52 (30/58)	75 (77/103)	34 (15/44)	79 (90/114)
Relapse[a] % (n/N)	14 (5/35)	10 (9/86)	25 (5/20)	9 (9/99)
EOT % (n/N)	60 (35/58)	86 (89/103)	48 (21/44)	89 (101/114)

a: Relapse rate was the proportion of patients with undetectable HCV-RNA at EOT and detectable HCV-RNA at EOF among patients who were undetectable at EOT and not missing EOF data.

b: The FAS consisted of all randomized patients (n=403) who received at least one dose of any study medication (PegIFNα2b, RBV, or BOC).

c: Previous Non-Responder = patient who failed to achieve SVR after at least 12 weeks of previous treatment with PegIFNα2b/RBV, but demonstrated a ≥ 2-$\log_{10}$ reduction in HCV-RNA by Week 12.

d: Previous Relapser = patient who failed to achieve SVR after at least 12 weeks of previous treatment with PegIFNα2b/RBV, but had undetectable HCV-RNA at the EOT.

e: Eleven patients were missing TW 4 assessment (HCV-RNA) and were not included in the Lead-In response results.

f: Sustained Virologic Response: The last available value in the period at and after FW 24. If there is no such value, the FW 12 value was carried forward.

Sustained Virologic Response Based on TW 8 HCV-RNA Results

Response-Guided Therapy based on TW 8 response is equally effective as adding BOC to the 48-week standard of care regimen. Forty-six percent (74/162) of patients in the BOC-RGT arm and 52 % (84/161) of patients in the BOC/PegIFNα2b/RBV-48 arm were early responders (patients with undetectable HCV-RNA at TW 8). Of the patients that were early responders, 71 patients were undetectable at TW 12 in the BOC-RGT arm and 81 patients were undetectable at TW 12 in BOC/PegIFNα2b/RBV-48 arm. Boceprevir-RGT early responders, who received 36 weeks of therapy (an initial 4 weeks of PegIFNα2b/RBV followed by 32 weeks of BOC with PegIFNα2b/RBV), had an SVR rate of 86 % (64/74) compared with an SVR rate of 88 % (74/84) in the matched population in the BOC/PegIFNα2b/RBV-48 arm who received 48 weeks of therapy (an initial 4 weeks of PegIFNα2b/RBV followed by 44 weeks of BOC with PegIFNα2b/RBV) (see Table 15).

Table 15: Sustained Virologic Response, End of Treatment, and Relapse Rates in the Experimental Arms with Undetectable or Detectable HCV-RNA at TW 8 in Previous Treatment Failures

	Undetectable HCV-RNA at TW 8		Detectable HCV-RNA at TW 8	
	BOC-RGT[a]	**BOC/PegIFNα2b/RBV-48**	**BOC -RGT[a]**	**BOC/PegIFNα2b/RBV-48**
SVR[b] %, (n/N)	86 (64/74)	88 (74/84)	40 (29/72)	43 (30/70)
EOT (Undetectable HCV-RNA) % (n/N)	97 (72/74)	96 (81/84)	56 (40/72)	57 (40/70)
Relapse[c] % (n/N)	11 (8/71)	8 (6/80)	24 (9/38)	21 (8/38)

a: BOC-RGT – Patients received PegIFNα2b/RBV for 4 weeks, then BOC 800 mg TID + PegIFNα2b/-RBV as follows: BOC 800 mg TID + PegIFNα2b/RBV for 32 weeks (patients with undetectable HCV-RNA at TW 8 (early responders) and TW 12) or BOC 800 mg TID + PegIFNα2b/RBV for 32 weeks followed by placebo + PegIFNα2b/RBV for 12 weeks (patients detectable HCV-RNA at TW 8 but subsequently negative by TW 12).

b: Sustained Virologic Response: The last available value in the period at and after FW 24. If there is no such value, the FW 12 value was carried forward.

c: Relapse rate was the proportion of patients with undetectable HCV-RNA at EOT and detectable HCV-RNA at EOF among patients who were undetectable at EOT and not missing EOF data.

In patients who were not early responders (patients with detectable HCV-RNA at TW 8), the SVR rate in the BOC-RGT arm was 40 % (29/72) compared with an SVR rate of 43 % (30/70) in the matched population in the BOC/PegIFNα2b/RBV-48 arm (see Table 15). Thirty-eight patients in the BOC-RGT arm and 37 patients in the BOC/PegIFNα2b/RBV-48 arm had detectable HCV-RNA at TW 8 but were subsequently undetectable at TW 12 (late responders). Boceprevir-RGT late responders, who received an initial 4 weeks of PegIFNα2b/RBV then 32 weeks of BOC with PegIFNα2b/RBV followed by 12 weeks of PegIFNα2b/RBV alone, had an SVR rate of 76 % (29/38) compared with an SVR rate of 62 % (23/37) in the matched population in the BOC/PegIFNα2b/RBV-48 arm, who received 4 weeks of PegIFNα2b/RBV followed by 44 weeks of BOC in addition to PegIFNα2b/RBV. These data support that, in late responders, 36 weeks of BOC with PegIFNα2b/RBV followed by 12 weeks of PegIFNα2b/RBV is adequate and that treatment with BOC may be shortened to 32 weeks in patients who have received previous therapy.

A difference was observed in the number of patients who achieved SVR between the BOC-RGT arm and the BOC/PegIFNα2b/RBV-48 arm. This difference is explained by imbalances in treatment response observed amongst patients in each arm who received identical therapy prior to TW 36.

Sustained Virologic Response Based on Baseline Factors

Sustained Virologic Response rates of patients in the BOC-RGT and BOC/PegIFNα2b/RBV-48 compared to patients who received PegIFNα2b/RBV alone with the following baseline factors were as follows: Baseline HCV-RNA > 400,000 IU/mL (57 % (88/155) and 66 % (102/154) vs. 19 % (14/74)), advanced liver disease (F3/4) (44 % (14/32) and 68 % (21/31) vs. 13 % (2/15)), cirrhotics (F4) (35% (6/17) and 77% (17/22) vs. 0% (0/10)), genotype 1a (53 % (50/94) and 64 % (61/96) vs. 24 % (11/46)), and genotype 1b (67 % (44/66) and 70 % (43/61) vs. 18 % (6/34)). Among patients who failed previous therapy with advanced liver disease (F3/4), the SVR rate was higher in patients who received four weeks of therapy with PegIFNα2b/RBV followed by 44 weeks of BOC/PegIFNα2b/RBV (68 %) compared to patients who received BOC-RGT (44 %). However, these conclusions were based on a small sample size of patients with advanced fibrosis.

DETAILED PHARMACOLOGY

Pharmacodynamics

Electrocardiogram (ECG) Evaluation

Thirty-six healthy adult subjects were enrolled into and 31 subjects completed a randomized, placebo- and active-controlled, multiple-dose, evaluator-blind, four-way, crossover study. Each treatment consisted of oral dosing for 5 days of: A) BOC 800 mg TID; B) BOC 1,200 mg TID; C) moxifloxacin- 400 mg Once Daily (QD); and D) placebo with a 7-day washout period between each treatment period. The moxifloxacin treatment group validated the study design since prolongation of mean QT/QTc was measured with this treatment. Boceprevir did not prolong the QTcF interval at the 800 mg (therapeutic dose) or the 1,200 mg dose or relative to placebo. Neither the 800 mg dose or the 1,200 mg dose of BOC was associated with clinically relevant effects on cardiac conduction.

At the mean maximum BOC exposures of 1,690 and 1,940 ng/mL, which were achieved at 2 hours postdose for the 800 and 1,200 mg doses, the mean increases in placebo-adjusted QTcF were 4.5 and 0.3 ms with the upper limits of the 95 % CI of 7.3 and 3.1 ms, respectively. The maximum observed mean increases in placebo-adjusted QTcF occurred at 4 hours post-dose, and were 5.8 and 2.9 ms with the upper limits of the 95 % CI of 8.7 and 5.7 ms, respectively. Therefore, in this study with demonstrated ability to detect small effects, the upper bound of the one-sided 95 % confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on individual correction method was below 10 ms, the threshold for regulatory concern. The dose of 1,200 mg yields a BOC maximum exposure increase of approximately 15 % which may not cover exposures due to co-administration with strong CYP3A4 inhibitors or use in patients with severe hepatic impairment. However, at the doses studied in the thorough QT study, no apparent concentration-QT relationship was identified. Thus, there is no expectation of a QTc effect under a higher exposure scenario.

When QTcF in men and women was analyzed separately, similar results were obtained. There was no difference between men and women when placebo and BOC at both the 800 mg dose and the 1,200 mg dose were compared.

Pharmacokinetics

General Pharmacokinetic Characteristics

The PK profile of BOC in healthy subjects, HCV-infected patients and population PK parameters are presented in Table 16. In general, the PK results were similar between healthy subjects and HCV patients.

Table 16: Pharmacokinetics of boceprevir in Healthy Subjects, HCV-Infected Patients and PPK Estimates

Pharmacokinetic Parameters	HCV Patients (800 mg)[a]	Population PK Estimates (HCV Patients; 800 mg)	Healthy Subjects (800 mg)[b]
C_{max} (ng/mL)	1,013	1,084	1,723
AUC (ng● h/mL)	4,403	4,642	5,408
C_{min} (ng/ml)	213	218	88
$T_{1/2}$ (h)	---	---	3
T_{max} (h)	2	1.90	2
CL/F (L/h)	182	172	159
Vc/F	207	196	---
Vd/F (L)	---	---	717

a: PPK individual prediction from sparse data
b: Parameters obtained using non-compartmental analysis

Absorption

Effects of Food on Oral Absorption

The PK parameters of BOC following administration under fasted and fed (high-fat) conditions in healthy subjects are presented in Table 17. Following administration with food to healthy subjects, BOC was rapidly absorbed with a median T_{max} of approximately 2.0 hours. *In vitro*, BOC has been shown to be a substrate of P-gp. There was no discernible dose-related effect on T_{max}. Steady-state mean BOC AUC, C_{max}, and C_{min} increased in a less than dose proportional manner and individual exposures overlapped substantially at 800 mg and 1,200 mg, suggesting diminished absorption at higher doses. The power log model shows an increase in exposure of 27 % to 38 % between 800 mg and 1,200 mg TID. Steady state was reached after approximately 1 day of TID dosing.

Table 17: Pharmacokinetic Parameters of boceprevir following Administration under Fasted and Fed (High-Fat) Conditions in Healthy Adult Subjects

Pharmacokinetic Parameters	Fasted	Fed (High-Fat Meal)	Ratio Estimate (%)	Confidence Interval (90 %)
AUC (ng● hr/Ml)	4,210	6,350	161	131-198
C_{max} (ng/ml)	1,370	1,710	148	102-216
T_{max} (hr)	1.5	3.5	---	---
$t_{1/2}$ (hr)	3.58	3	---	---

Administration with food increased the oral bioavailability of BOC relative to the fasted state, by 40 % to 60 % based on AUC. Administration with food also modestly delayed median BOC T_{max} from approximately 1 hour to approximately 2 hours. Meal type, and timing of meal administration, did not notably affect the increase in exposure.

Distribution

Mean Vd/F in fed subjects showed extensive distribution with a mean Vd/F of approximately 717 L (n = 71). Boceprevir is not highly bound to human plasma proteins. The mean unbound fraction of BOC in plasma was similar between healthy subjects and subjects with End-Stage Renal Disease (ESRD).

Metabolism

Clinical data show that BOC is rapidly metabolized to an inactive, ketone-reduced metabolite. This metabolite has been shown to be inactive as a serine PI in an *in vitro* assay using recombinant HCV NS3/4A protease. The median T_{max} for this metabolite was approximately 3 hours. This metabolite is present in plasma in a ratio to BOC of approximately 4:1 at a dose of 800 mg. Based on all known *in vitro* data and clinical drug-drug interactions studies; metabolism clinically appears to be primarily via the AKR enzymes and to a minor extent via CYP3A4/5-mediated oxidation. Profiling of drug-derived material in plasma, urine and feces showed that ^{14}C-BOC was extensively metabolized by humans. Over sixty metabolites were detected in humans. The metabolic modification can be assigned to one or more of the five regions in the molecule. The major biotransformation pathway involved reduction of the second carbonyl group at the carboxamide terminus, which accounted for at least ~ 22 % of the dose excreted in urine and feces. Other metabolic pathways included oxidation, cleavage, dimerization, and a combination of these processes, including reduction. Most of the oxidative metabolites were excreted in feces. Approximately 8 % of the dose was detected in feces as unchanged drug.

Excretion

Boceprevir was eliminated with a mean plasma $t_{½}$ of approximately 3.0 hours (n = 71). The mean $t_{½}$ tended to be variable between studies and was associated with a high coefficient of variation (% CV) of 90 %. The mean CL/F of BOC across several studies was approximately 159 L/h. Accumulation of BOC was minimal with multiple days of TID dosing and steady state was reached after approximately 1 day of TID dosing. In a clinical study with ^{14}C-BOC a mean total of 88.2 % of the radioactive dose was recovered in the urine and feces 168 hours after a single oral administration of 800 mg. Radioactivity recovered in the urine and feces accounted for 9.28 % and 78.9 % of the dose, respectively with approximately 3 % and 8 % of the dosed radiocarbon eliminated as BOC in urine and feces, respectively. Most of the radioactivity was excreted in the urine within the first 12 hours. Therefore it is a reasonable assumption that most of the metabolites excreted in feces following administration of ^{14}C-BOC must be derived from absorbed drug.

Drug-Drug Interactions

Boceprevir is a strong inhibitor of CYP3A4/5. Drugs metabolized primarily by CYP3A4/5 may have increased exposure when administered with BOC, which could increase or prolong their therapeutic and adverse effects (see **CONTRAINDICATIONS**). Boceprevir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 *in vitro*. In addition, BOC does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4/5 *in vitro*.

Boceprevir is primarily metabolized by AKR. In drug interaction trials conducted with AKR inhibitors diflunisal and ibuprofen, BOC exposure did not increase to a clinically significant extent. Boceprevir may be co-administered with AKR inhibitors.

Boceprevir is partly metabolized by CYP3A4/5. It is also a substrate for P-glycoprotein (P-gp). Co-administration of BOC with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to BOC. Drugs that are potent CYP3A4/5 inducers may significantly reduce BOC plasma concentrations, which may be associated with reduced efficacy (see **CONTRAINDICATIONS**).

Drug interaction studies were performed with BOC and drugs most likely to be co-administered with BOC. The effects of co-administration of other drugs on the PK (AUC, C_{max} and C_{min}) of BOC are summarized in Table 18 while the effects of BOC on other drugs are summarized in Table 19. For information regarding clinical recommendations, see **DRUG INTERACTIONS**.

Table 18: Drug Interactions; PK Parameters for boceprevir in the Presence of Co-administered Drugs

	Dose/Schedule		n	Change in PK	Ratio Estimate (90 % CI) of BOC PK Parameters With/Without Co-administered Drug. No Effect=1.00		
	Co-administered Drug	BOC			C_{max}	AUC	C_{min}
Co-Administration with Antifungals							
ketoconazole	400 mg BID	400 mg Single dose	12	↑	1.41 (1.00-1.97)	2.31 (2.00-2.67)	N/A
Co-Administration with Other Antivirals							
efavirenz	600 mg daily	800 mg TID	12	↑	0.92 (0.78-1.08)	0.81 (0.75-0.89)	0.56 (0.42-0.74)
ritonavir	100 mg daily	400 mg TID	12	↓	0.73 (0.57-0.93)	0.81 (0.73-0.91)	1.04 (0.62-1.75)
tenofovir	300 mg daily	800 mg TID	17	↔	1.05 (0.98-1.12)	1.08 (1.02-1.14)	1.08 (0.97-1.20)
PegIFNα2b	1.5 mcg/kg SC weekly	400 mg TID	10	↔	0.88 (0.66-1.18)	1.00 (0.89-1.13)	N/A
Co-Administration with Other Drugs							
ibuprofen	600 mg TID	400 mg Single dose	12	↔	0.94 (0.67-1.32)	1.04 (0.90-1.20)	N/A
diflunisal	250 mg BID	800 mg TID	12	↔	0.86 (0.56-1.32)	0.96 (0.79-1.17)	1.31 (1.04-1.65)

SC = subcutaneous

Table 19: Drug Interactions; PK Parameters of Co-administered Drugs in the Presence of boceprevir

	Dose/Schedule		n	Change in PK	Ratio Estimate (90 or 95 % CI) of Co-administered Drug PK Parameters With/Without BOC. No Effect=1.00	
	Co-administered Drug	BOC			C_{max}	AUC
Co-Administration with Sedative/Hypnotics						
midazolam	4 mg single oral dose	800 mg TID	12	↑	5.30 (4.66-6.03)	2.77 (2.36-3.25)
Co-Administration with Oral Contraceptives						
drospirenone/ethinyl estradiol	drospirenone: 3 mg daily ethinyl estradiol: 0.02 mg daily	800 mg TID	16	↑ ↓	drospirenone: 1.99 (1.87-2.11) ethinyl estradiol: 0.76 (0.73-0.79)	drospirenone: 1.57 (1.46-1.70) ethinyl estradiol: 1.00 (0.91-1.10)
Co-Administration with Other Antivirals						
tenofovir	300 mg daily	800 mg TID	17	↔	1.05 (1.01-1.09)	1.32 (1.19-1.45)
efavirenz	600 mg daily	800 mg TID	12	↑	1.20 (1.15-1.26)	1.11 (1.02-1.20)
PegIFNα2b	1.5 mcg/kg SC weekly	400 mg TID	10	↔	0.99[a, b] (0.83-1.17)	N/A

a: 0-168 hours
b: Reported AUC is 200 mg and 400 mg cohorts combined.
SC = subcutaneous

Population Pharmacokinetics

Population PK analysis in Phase 3 studies systemically checked for significant effects on systemic clearance, volume of distribution and absorption rates by the following characteristics: health status (HCV subject vs healthy subject), demographics (sex, black race, Asian race, age, weight, and BMI), hepatic function (AST, ALT), and renal function (creatinine clearance). Systemic clearance and volume of distribution were not influenced by demographics, measures of renal function or hepatic function, except for sex on clearance and absorption rate and of health status on central volume. These effects were well within the range of estimated inter-individual and intra-individual variability in BOC exposure, and were therefore not considered clinically relevant.

Special Populations and Conditions

Sex, Age, Body Weight, Height, and Body Mass Index

In the Phase 2 PPK analysis, sex, body weight, height, and BMI had no significant effect on BOC CL/F or Vd/F; however, an age effect was observed against CL/F. The estimated age effect on CL/F was -0.291 suggesting minimal difference in CL/F attributable to age. In the Phase 3 PPK analysis, no age effect was noted. However, effects of sex on clearance and absorption rate were noted. These effects were well within the range of estimated inter-individual and intra-individual variability in BOC exposure, as well as within clinical bounds of comparability, and were therefore not considered clinically relevant.

Race

At the target clinical dose of 800 mg TID (with food), BOC was administered for seven days to six paired healthy Caucasian and Japanese subjects (matched for age, weight and height). In general, the PK parameters of BOC following single and multiple doses of BOC were similar between Caucasian and Japanese subjects, under both fed and fasting conditions, with no notable accumulation of BOC in plasma and similar CL/F between Caucasian and Japanese subjects. At the target clinical dose of 800 mg TID administered with food, steady-state mean AUC and C_{max} in Japanese were 14 % and 5 % lower, respectively compared with matched-Caucasian subjects and are well within the apparent lower bounds of clinical significance. Dose-normalized pooled data analysis indicated that both the steady-state mean AUC and C_{max} of BOC increased in a less than dose-proportional manner in both Japanese and Caucasian subjects after receiving multiple doses of 200 mg, 400 mg, and 800 mg. Food increased exposure of BOC compared with fasted conditions in both Caucasian and Japanese subjects, with the increased exposure more apparent at higher dose levels. The mean ratio estimate for AUC at a single dose of 800 mg ranged from 142 % to 196 % fed vs. fasted. Boceprevir should be administered with food, and no modification of BOC dose is required for persons of Japanese descent. In a Phase 1 study, mean AUC and C_{max} were lower in Black compared with non-Black subjects. However, the sample size in this study was very small. The Phase 2 PPK analysis revealed that race had no significant effect on BOC CL/F or Vd/F. The non-Caucasian subjects in this subanalysis were not specific for Black subjects as there were too few Blacks, but covered all non-Caucasian races. The Phase 3 PPK analysis indicated that Black or Asian race was not a significant covariate for BOC PK.

Hepatic Insufficiency

A study was performed to assess the safety and PK of BOC in subjects with varying degrees of hepatic insufficiency. Adult non HCV-infected males and females with mild (Child-Pugh score 5-6), moderate (Child-Pugh score 7-9), severe (Child-Pugh score 10-12) impairment and matched subjects with normal hepatic function were administered a single 400 mg dose of BOC in the original formulation under fasted conditions. With increasing severity of liver impairment, a trend toward increased mean area under the plasma concentration–time curve from last quantifiable sample ($AUC_{(tf)}$) and mean C_{max} of BOC was observed (see Table 20). Mean CL/F values in subjects with moderate and severe hepatic impairment were decreased. However, mean CL/F values remained in the range of mean CL/F seen in healthy subjects from other studies. Certain conditions of this trial, fasted dosing, a less than therapeutic dose, non-final formulation, limited the generalizability of the conclusions.

Table 20: PK Parameters of $AUC_{(tf)}$ and C_{max} of Hepatically Impaired Subjects Compared to Healthy Subjects for the boceprevir Active Diastereoisomer 534128

PK Parameter	Group	n	LS Mean	Treatment Comparison	Ratio Estimate %	90 % CI
AUC(tf) (ng*hr/mL)	Mild	6	1,009	Mild vs. Healthy	107	75-152
	Moderate	6	1,240	Moderate vs. Healthy	132	93-187
	Severe	6	1,361	Severe vs. Healthy	145	102-205
	Healthy	6	941	--	--	--
C_{max} (ng/mL)	Mild	6	295	Mild vs. Healthy	115	71-188
	Moderate	6	327	Moderate vs. Healthy	128	79-208
	Severe	6	413	Severe vs. Healthy	162	99-263
	Healthy	6	256	--	--	--

Estimates of steady-state maximum AUC and C_{max} parameters of patients infected with HCV in the Phase 3 studies were 9,715 ng·h/mL and 2,377 ng/mL, respectively. The Phase 3 PPK analysis-showed that hepatic dysfunction was not a significant covariate for BOC PK. Based on these data, no dose adjustment of BOC is required for subjects with hepatic impairment. However, because PegIFNα2b/RBV is contraindicated in the hepatically impaired population, the use of BOC with PegIFNα2b/RBV is also contraindicated in this population.

Renal Insufficiency

In a study with ^{14}C-BOC, drug-derived radiocarbon was mainly eliminated via the feces, with < 10 % recovered in urine, indicating renal clearance is a minor pathway. A study was performed to assess the safety, tolerability and PK of BOC in subjects with varying degrees of renal insufficiency. Male and female, non HCV-infected hemodialysis-dependent ESRD subjects and matched subjects with normal renal function were administered a single 800 mg dose of BOC. ESRD subjects were dosed prior to dialysis (Day 1) and 4 hours prior to dialysis (Day 4). The difference in exposure compared with healthy subjects was not clinically relevant, and dialysis did not affect the PK of BOC (see Table 21). As there were no differences in exposure in the most severely renally impaired subjects, no dose adjustment of BOC is required in patients with any degree of renal impairment.

Table 21: Mean (CV, %) Plasma PK Parameters of boceprevir following a Single Oral Dose of boceprevir 800 mg to Healthy Subjects and to Patients with ESRD

Parameter	Healthy Subjects	ESRD Patients	
		Day 1	Day 4
AUC(tf) (ng·hr/mL)	5,710 (50)	5,100 (53)	5,000 (43)
AUC(I) (ng·hr/mL)	5,760 (50)	5,150 (53)	5,030 (43)
Cmax (ng/mL)	1,730 (54)	1,340 (52)	1,420 (35)
T_{max}[a] (hr)	2.00 (2.00-4.00)	4.00 (1.00-6.00)	2.00 (1.32-2.00)
$t_{½}$ (hr)	1.73 (21)	2.20 (60)	1.72 (43)
CL/F (L/hr)	178 (55)	193 (50)	183 (38)
Vd/F (L)	417 (47)	637 (89)	495 (86)

a: Median (range)

Animal Pharmacology

Single-dose administration of ^{14}C-BOC under fasted conditions showed that concentrations of radioactivity in plasma were greater than those in whole blood, and the comparison of radioactivity concentrations in plasma and blood indicated a minor partitioning into the cellular components of blood. Mean exposure to BOC in plasma accounted for approximately 26.2 % of the total plasma radioactivity. Individual plasma to blood radioactivity concentration ratios remained constant over the quantifiable intervals following dosing. Tissue distribution was examined by quantitative-whole-body autoradiography in rats administered a single, oral dose of 25 mg/kg ^{14}C-BOC. Peak radiocarbon concentrations were observed in blood and most tissues at 0.5 hours postdose and declined to below quantifiable limits by 24 hours postdose. The highest radiocarbon concentrations were measured in liver, bladder wall, kidneys, and prostate gland. ^{14}C-BOC -derived radiocarbon was not detected in the brain or spinal cord. There were no qualitative differences in tissue distribution between male and female or between pigmented and non-pigmented rats. In preclinical studies, the percent binding increased as the concentration of BOC decreased in plasma from several species. In studies in rats, dogs, and monkeys administered ^{14}C-BOC, the main route of elimination was also via the feces, due to a combination of biliary excretion and, for orally dosed animals, unabsorbed drug. Less than 10 % of administered radiocarbon was recovered in urine. Absolute bioavailability ranged from 26 % to 34 % in fasted mice, rats, and dogs and was 4 % in monkeys. On average 71 % of the excreted radioactivity in feces was due to metabolites.

Safety pharmacology studies were conducted to evaluate the effect of BOC on the cardiovascular, respiratory, central nervous, gastrointestinal and renal systems. No effects on cardiac function or electrocardiography parameters were observed in dogs with oral doses of 3 or 50 mg/kg BOC. The corrected QT interval (QTc) revealed no significant difference between BOC (75 or 200 mg/kg) and vehicle in cynomolgus monkeys. There were no statistically significant changes in respiratory rate, tidal volume or minute volume with single oral gavage doses of 25, 75 or 200 mg/kg of BOC in rats. Boceprevir did not demonstrate any drug-related effect on renal function, gastric emptying or intestinal transit. The NOAEL for central nervous system pharmacological activity in rats is 200 mg/kg based on the lack of BOC -related changes.

MICROBIOLOGY

Antiviral Activity in Cell Culture

The antiviral activity of BOC was evaluated in a biochemical assay for slow binding inhibitors of NS3/4A protease and in the HCV replicon system. The IC_{50} and IC_{90} values for BOC were approximately 200 nM and 400 nM, respectively, in a 72-hour cell culture assay. Loss of replicon RNA appears to be first-order with respect to time of treatment. Treatment at IC_{90} for 72 hours resulted in a 1-log drop in replicon RNA. Prolonged exposure resulted in a 2-log decrease in RNA levels by Day 15.

Boceprevir cell culture anti-HCV activity was approximately 2-fold lower for an HCV replicon derived from a single genotype 1a isolate, relative to the 1b isolate-derived replicon. In replicon assays, BOC had approximately 2-fold reduced activity against a genotype 2a isolate relative to genotype 1a and 1b replicon isolates. In a biochemical assay, BOC had approximately 3- and 2-fold reduced activity against NS3/4A proteases derived from single isolates representative of HCV genotypes 2 and 3a, respectively, relative to a genotype 1b-derived NS3/4A protease. The

presence of 50 % human serum reduced the cell culture anti-HCV activity of BOC by approximately 3-fold.

Evaluation of varying combinations of BOC and interferon alfa-2b that produced 90 % suppression of replicon RNA showed additivity of effect; no evidence of synergy or antagonism was detected.

Resistance

***In vitro* Studies**

The activity of BOC against the HCV NS3/4A protease or genotype 1b replicon was reduced (2- to 10- fold) by the following amino acid substitutions in the NS3/4A protease domain: V36A/I/M, Q41R, F43C/S, T54A/S, V55A/I, R155K/M/Q, V158I, V170A/T and M175L. A greater than 15-fold reduction in BOC anti-HCV activity was conferred by the substitutions T54C, R155G/I/T and A156S/T/V. The fold decrease in BOC anti-HCV activity conferred by double resistance-associated substitutions was approximately equal to the product of that for the individual substitutions.

Clinical Virology Studies

A pooled analysis was conducted to explore the association between the detection of baseline NS3/4A amino acid polymorphisms and treatment outcome in the two Phase 3 studies, SPRINT-2 and RESPOND-2. Resistance associated polymorphisms were detected in viruses from 6.7 % of subjects at baseline; 5.4 % had genotype 1a virus and 1.3 % had genotype 1b viruses. Overall, the presence of baseline RAVs alone did not appear to have a notable association with treatment response in patients who received the combination of BOC with PegIFNα2b/RBV.

In a pooled analysis of patients who are previously untreated and patients who have failed previous therapy who received four weeks of PegIFNα2b/RBV followed by BOC 800 mg TID in combination with PegIFNα2b/RBV in two Phase 3 studies, post-baseline RAVs were detected in 53 % of non-SVR patients. In patients treated with BOC, interferon responsiveness (as defined by $\geq$ 1-$\log_{10}$ decline in viral load at TW 4) was associated with detection of fewer RAVs, with 6 % of these patients having RAVs compared to 41 % of patients with < 1-$\log_{10}$ decline in viral load at TW 4 (poorly interferon responsive). In patients treated with BOC with post-baseline samples analyzed for RAVs, interferon responsiveness was associated with detection of fewer RAVs, with 31 % of these patients having post-baseline RAVs compared to 68 % of patients with < 1-$\log_{10}$ decline in viral load at TW 4. There was no significant difference in the number of non-SVR patients with RAVs detected that received response guided therapy, compared to those that received 48 weeks of BOC/PegIFNα2b/RBV. The RAVs most frequently detected post-baseline (> 25 % of subjects) in non-SVR subjects were amino acid substitutions V36M (61 %) and R155K (68 %) in subjects with genotype 1a viruses and T54A (42 %), T54S (37 %), A156S (26 %) and V170A (32 %) in subjects with genotype 1b viruses.

Persistence of Resistance-Associated Mutations

Data from an ongoing, long-term follow-up study of subjects who did not achieve SVR in Phase 2 trials with BOC, with a median duration of follow-up of approximately 2 years, indicate that HCV populations harbouring certain post-baseline, BOC-treatment-emergent substitutions may decline in relative abundance over time. However, among those subjects with available data, one or more BOC-treatment-emergent substitutions remained detectable with a population-based

sequencing assay in 25% of subjects after 2.5 years of follow-up. The most common NS3/4A substitutions detected after 2.5 years of follow-up were T54S and R155K. The lack of detection of a substitution based on a population-based assay does not necessarily indicate that viral populations carrying that substitution have declined to a background level that may have existed prior to treatment. The long-term clinical impact of the emergence or persistence of BOC-resistance-associated substitutions is unknown. No data are available regarding the efficacy of BOC among subjects who were previously exposed to BOC, or who previously failed treatment with a BOC-containing regimen. The majority of the patients in the long-term follow-up study were not dosed with the indicated BOC regimen.

Effect of Baseline HCV Polymorphisms on Treatment Response
A pooled analysis was conducted to explore the association between the detection of baseline NS3/4A amino acid polymorphisms and treatment outcome in the two Phase 3 studies, SPRINT-2 and RESPOND-2.

Baseline resistance associated polymorphisms were detected in 7 % of subjects by a population-based sequencing method. Overall, the presence of these polymorphisms alone did not impact SVR rates in subjects treated with BOC. However, among subjects with a relatively poor response to PegINFα2b/RBV during the 4-week lead-in period, the efficacy of BOC appeared to be reduced for those who had V36M, T54A, T54S, V55A or R155K detected at baseline. Subjects with these baseline polymorphisms and reduced response to PegINFα2b/RBV represented approximately 1 % of the total number of subjects treated with BOC.

Cross-Resistance
Many of the treatment-emergent NS3/4A amino acid substitutions detected in BOC-treated subjects who did not achieve SVR in the Phase 3 clinical trials have been demonstrated to reduce the anti-HCV activity of other HCV NS3/4A Protease Inhibitors (PIs). The impact of prior exposure to BOC or treatment failure on the efficacy of other HCV NS3/4A PIs has not been studied. The efficacy of BOC has not been established for patients with a history of exposure to other NS3/4A PIs. Cross-resistance is not expected between BOC and interferons, or BOC and RBV.

Pharmacogenomics
Genetic variance near the gene encoding interferon-lambda-3 (*IL28B rs12979860*, C to T change) has been demonstrated to be a strong predictor of response to PegINFα2b/RBV. *IL28B rs12979860* was genotyped in 653 of 1048 (62 %) subjects in SPRINT-2 (previously untreated) and 259 of 394 (66 %) subjects in RESPOND-2 (previous treatment failure) (see **CLINICAL TRIALS**).

Overall, among the patients that received at least one dose of placebo or BOC (Modified-Intent-to-Treat population) plus PegINFα2b/RBV for 48-weeks, the SVR rates tended to be lower in patients with the C/T and T/T genotypes when compared to the C/C genotype of both Previously Untreated Patients and Previous Treatment Failures. The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences in demographic or clinical characteristics of the sub-study population relative to the overall trial population.

Table 22: Sustained Virologic Response Rates by *IL28B rs12979860* Genotype

Clinical Study	*IL28B rs12979860* Genotype	SVR, % (n/N)		
		PegIFNα2b/RBV-48[a]	BOC/PegIFNα2b/RBV (RGT)*	BOC/PegIFNα2b/RBV -48[a]
SPRINT-2 (Previously Untreated Subjects)	C/C	78 (50/64)	82 (63/77)	80 (44/55)
	C/T	28 (33/116)	65 (67/103)	71 (82/115)
	T/T	27 (10/37)	55 (23/42)	59 (26/44)
RESPOND-2 (Subjects Who Have Failed Previous Therapy)	C/C	46 (6/13)	79 (22/28)	77 (17/22)
	C/T	17 (5/29)	61 (38/62)	73 (48/66)
	T/T	50 (5/10)	55 (6/11)	72 (13/18)

a: For description of each treatment arm, see **CLINICAL TRIALS**.

TOXICOLOGY

Carcinogenicity and Mutagenicity

Two-year carcinogenicity studies in mice and rats were conducted with BOC. Mice were administered doses up to 650 mg/kg. Rats were administered doses of up to 125 mg/kg in males and 100 mg/kg in females. At the high dose of 650 mg/kg in female mice, the incidence of hepatocellular adenomas was increased at systemic exposures 5.7−fold of those in humans at the recommended 800 mg TID clinical dose. There were no increases in mortality or malignancy associated with the hepatocellular adenomas. Induction of CYP450 enzymes has been demonstrated previously in mice administered BOC, and liver tumours are a recognized sequelae with chronic exposure to an enzyme inducer. There were no increases in the incidence of tumours in male mice at any dose in the study. In rats, no treatment-related increase in adenomas or carcinomas occurred at systemic exposures similar to the human exposure at the recommended 800 mg TID clinical dose (rat-to-human multiple of ~0.9-fold). The clinical relevance of the hepatocellular adenomas observed in female mice, if any, is unknown.

Boceprevir was not mutagenic or genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, human peripheral blood lymphocyte and mouse micronucleus assays.

Reproductive and Developmental Toxicity

Following a single, oral dose of 30 mg/kg ^{14}C-BOC, medicine-derived radiocarbon was transferred into the milk of lactating, 12-day postpartum rats. Peak systemic concentrations of medicine-derived radiocarbon in nursing pups were over 100-fold lower than in the mothers. Exposure to medicine-derived materials in nursing human infants is estimated to be less than 1 % of the dose.

In rats, BOC induced reversible effects on fertility and early embryonic development in female rats with a No Effect Level (NEL) of 75 mg/kg. At this dose, the rat-to-human exposure multiple is 1.3−fold higher than the systemic human exposure at the recommended human therapeutic dose of 800 mg TID. Decreased fertility was also observed in male rats, most likely as a consequence of testicular degeneration (included Sertoli cell vacuolation, atrophy of the seminiferous tubule epithelium, epididymal cellular debris, hypospermia of the epididymides, spermatid degeneration, soft testes, and decreased sperm count and motility), with evidence of partial reversibility and a NEL of 15 mg/kg (which represents a rat-to-human exposure multiple of less than 1-fold the human exposure at the human therapeutic dose of 800 mg TID). In juvenile rats, the mean age of attainment of balanopreputial separation was minimally higher compared to the control group (46.1 compared to 44.4 days). This finding was also associated with testicular/epididymal findings similar to those observed in adult rats, and included lower mean epididymides and testes weights. The NEL for these findings represents a rat-to-human exposure multiple of less than 1-fold the human exposure at the human therapeutic dose of 800 mg TID. Testicular degeneration has not been observed in mice or monkeys and therefore is considered species-specific to rats. Additionally, clinical monitoring of the surrogate marker inhibin-B, as well as semen analysis has revealed no evidence that these findings are clinically relevant in human patients.

In juvenile rats, BOC induced reversible hyperplasia of thyroid gland follicular cells and higher liver weights, with a NEL that represents a rat-to-human exposure multiple of less than 1-fold the human exposure at the human therapeutic dose of 800 mg TID. Since no BOC-related thyroid hyperplasia has been observed in any adult rat, mouse or monkey studies, these changes are considered age- and species-specific to the juvenile rat, and not a safety concern for humans. Thyroid function tests have been included in BOC clinical studies with no evidence of BOC-related thyroid changes.

Acute Toxicity

Boceprevir has a low order of oral single-dose toxicity. No adverse effects were observed in rats at doses of 2,000 mg/kg in females and 1,000 mg/kg in males. In monkeys, no adverse effects were observed at doses up to 250 mg/kg and only minor clinical signs of emesis and abnormal stool findings were observed at 500 and 1,000 mg/kg. No adverse effects were observed in dogs at a dose of 100 mg/kg and the only findings observed at the highest dose tested of 200 mg/kg were emesis and abnormal stool findings.

Chronic Toxicity

Boceprevir-related nonclinical toxicology findings tend to be dose-related and/or species-specific in nature; and occur at exposures that are slightly higher than or similar to the clinical therapeutic dose. Targets identified in nonclinical studies consist of the gall bladder, liver, reproductive tract, and the activated partial thromboplastin time (APTT) coagulation parameter; and were primarily observed in rodents. None of these nonclinical findings have been identified clinically.

Discolored gall bladder was observed in the 2-year mouse carcinogenicity study with no histopathologic correlate, inflammation, evidence of concretions, long-term impact to gall bladder integrity or gall bladder tumors. In shorter duration mouse studies (at higher doses and exposures) and in monkey studies, no gall bladder discoloration was observed. The NEL for this finding represents a mouse-to-human exposure multiple of less than 1-fold the human exposure

at the human therapeutic dose of 800 mg TID. There have been no BOC-related clinical AEs suggestive of impaired gall bladder function.

Nonclinical toxicology findings related to the liver consisted of focal neutrophilic infiltrates (mice), single cell hepatocyte necrosis (mice), pigment accumulation in liver macrophages (mice), and multinucleated hepatocytes (male rats). With the exception of the multinucleated hepatocytes, all liver-related finding NELs represent mouse-to-human or rat-to-human exposure multiples similar to or greater than the human exposure at the human therapeutic dose of 800 mg TID. Liver function tests have revealed no evidence of clinical concern.

Increases in the coagulation parameter APTT have been observed in monkeys. There were no changes in other clinical pathology parameters that would be suggestive of hemorrhage, or gross pathology evidence of hemorrhage that would indicate a defect in hemostasis. The NEL for this finding represents a monkey-to-human exposure multiple of less than 1-fold the human exposure at the human therapeutic dose of 800 mg TID. APTT levels have been monitored in the clinic, and no clinically meaningful effects have been identified.

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PART III: CONSUMER INFORMATION

VICTRELIS™
boceprevir

This leaflet is part III of a three-part "Product Monograph" published when VICTRELIS™ (boceprevir) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VICTRELIS™. Contact your doctor or pharmacist if you have any questions about the drug.

Since you are taking VICTRELIS™ with peginterferon alpha/ribavirin, also read the leaflet related to these medications.

ABOUT THIS MEDICATION

What the medication is used for:
VICTRELIS™ is a prescription medicine used with peginterferon alpha plus ribavirin to treat chronic (lasting a long time) hepatitis C genotype 1 infection in adults who have not been previously treated or who have failed previous therapy. Patients with hepatitis C have the virus in their blood and in their liver.

It is not known if VICTRELIS™ is safe and effective when used in children (< 18 years of age).

What it does:
VICTRELIS™ is a medicine called a Hepatitis C Virus Protease Inhibitor that directly targets Hepatitis C Virus to reduce the amount of virus in your body.

When it should not be used:
Do not use VICTRELIS™ in combination with peginterferon alpha/ribavirin:

- if you are hypersensitive (allergic) to boceprevir or to any of the excipients (see ***What the non-medicinal ingredients are***);
- if you have certain types of hepatitis (autoimmune hepatitis);
- if you have advanced, uncontrolled liver disease (other than hepatitis C);
- if you are taking certain medicines. For more information about medicines that you should not take while using VICTRELIS™, please see ***Interactions with this Medication***;
- if you or your partner are pregnant.

What the medicinal ingredient is:
boceprevir

What the non-medicinal ingredients are:
croscarmellose sodium, gelatin, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pre-gelatinized starch, red iron oxide, shellac, sodium lauryl sulfate, titanium dioxide, yellow iron oxide

What dosage forms it comes in:
Each hard capsule contains 200 mg of boceprevir.

WARNINGS AND PRECAUTIONS

BEFORE you use VICTRELIS™, talk to your doctor or pharmacist if:

- you have ever had certain blood disorders such as anemia or neutropenia;
- you have liver problems other than hepatitis C infection;
- you are breastfeeding. It is not known if VICTRELIS™ passes into breast milk and whether it could harm your baby;
- you have Human Immunodeficiency Virus (HIV), any immunity problems, or have had an organ transplant;
- you have any other medical condition; or
- you are using any other medications.

VICTRELIS™ may cause a Reduction of Red Blood Cells a condition known as anemia, or a reduction of neutrophils (a type of white blood cell) a condition known as neutropenia. Anemia or neutropenia may be increased when VICTRELIS™ is added to your ribavirin therapy. Therefore, your healthcare provider will be checking your blood counts periodically for possible decreases in your blood cell counts. Depending on the medications that you are taking, your healthcare provider may make changes to your current medicines or prescribe additional medicines to treat your anemia, or neutropenia.

VICTRELIS™ may cause serious side effects when taken with other medications. It is important to know the medicines that should not be taken with VICTRELIS™.

Do not take the combination of VICTRELIS™ with peginterferon alpha/ribavirin if you or your partner are pregnant. Ribavirin may cause birth defects or death of your unborn baby. Ribavirin should not be taken by women who are pregnant and pregnancy should be avoided during use and up to 6 months after the last dose of ribavirin. As systemic (e.g., oral, topical…) hormonal contraceptives may not work as well while taking VICTRELIS™, use of 2 alternative methods of contraception, such as barrier method and intrauterine devices during treatment with VICTRELIS™ and ribavirin. If your healthcare provider has prescribed ribavirin as part of your treatment, read the ribavirin leaflet and discuss with your doctor.

Do not take VICTRELIS™ alone to treat Chronic Hepatitis C infection. VICTRELIS™ should only be used with other medicines, ribavirin and peginterferon alpha, to treat Chronic Hepatitis C infection.

INTERACTIONS WITH THIS MEDICATION

Do not take VICTRELIS™ if you take:

- alfuzosin - used to treat enlarged prostrate;
- amiodarone, propafenone and quinidine - used for heart beat problems;
- astemizole[1], terfenadine[1] - used to treat allergies, hives, itching and watery eyes;
- birth control pills that contain drospirenone;
- carbamazepine, phenobarbital, phenytoin - used to treat seizures and nerve pain;
- cisapride[1] – used to help with digestion;
- ergot-containing medicines used to treat migraines, such as:
  - ergotamine,
  - dihydroergotamine,
  - ergonovine,
  - methylergonovine;
- lovastatin, simvastatin - used for lowering high cholesterol and triglycerides;
- oral midazolam, oral triazolam - used to help you sleep;
- pimozide – used for mental health problems;
- rifampin – used to treat tuberculosis or meningitis;
- sildenafil and tadalafil - used for the treatment of pulmonary arterial hypertension;
- St. John's Wort - an herbal product used to help with your mood.

Tell your doctor if you are taking any of the following medications as they may interact with VICTRELIS™. The dosage of one or the other may have to be changed or the medication avoided:

- atorvastatin, bepridil, bosentan, budesonide, buprenorphine, colchicine, cyclosporine, desipramine, dexamethasone, digoxin, felodipine, fluticasone, fluvastatin, methadone, nicardipine, nifedipine, pravastatin, rifabutin, rosuvastatin, salmeterol, sirolimus, tacrolimus, trazodone, and warfarin

PROPER USE OF THIS MEDICATION

- Take VICTRELIS™ **exactly** as your healthcare provider tells you. Your healthcare provider will tell you how much to take and when to take it.
- **Always take VICTRELIS™ with food (a meal or a snack, such as a piece of fruit or crackers).**
- Each dose (four 200 mg capsules) of VICTRELIS™ should be taken 7 to 9 hours apart.

Usual Adult Dose:
VICTRELIS™ 800 mg Three Times Daily will be used in combination with peginterferon alpha/ribavirin. VICTRELIS™ will only be added to the treatment from the start of the fifth week, i.e. the day of your week 4 visit. The total duration of your treatment will depend on the way in which your virus responds to treatment.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of VICTRELIS™ and it is less than 2 hours before the next dose is due, the missed dose should be skipped. If you miss a dose and it is more than 2 hours before the next dose is due, take the missed dose with food and continue the normal dosing schedule. Do not double the next dose. If you have questions about what to do, call your healthcare provider.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

VICTRELIS™ may cause serious side effects, including:

- **Blood problems.** VICTRELIS™ can cause low red cell counts (anemia) or low neutrophil (neutropenia), which is a type of white blood cell, and low platelet counts (thrombocytopenia). In some people, these blood counts may fall to dangerously low levels.

Tell your provider right away if you have any side effect that bothers you or that does not go away.

The most common side effects of VICTRELIS™ in combination with ribavirin and peginterferon alpha include:

[1] Please note that cisapride, astemizole and terfenadine are no longer available on the Canadian market.

- fatigue, low red blood cell count (anemia), change in sense of taste, nausea, headache, diarrhea, vomiting, abdominal pain, fever, muscle and joint pain, weight loss, difficulty in sleeping, and dry skin

- fatigue, dizziness, fainting changes in blood pressure, and blurred vision can occur, so be cautious before driving or operating heavy machinery.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Very common	Blood problems: low red cell counts (anemia) which may lead to tiredness, headaches, shortness of breath when exercising, dizziness and looking pale.		√	
	Blood problems: low white blood cell counts (neutropenia) which may lead to an increased risk of getting infections.		√	

This is not a complete list of side effects. For any unexpected effects while taking VICTRELIS™, contact your doctor or pharmacist.

Since you are taking VICTRELIS™ with peginterferon alpha/ribavirin, also read the leaflet related to these medications.

HOW TO STORE IT

VICTRELIS™ Capsules should be refrigerated at 2°C – 8°C until dispensed by a pharmacist. For patient use, refrigerated capsules of VICTRELIS™ can remain stable until the expiration date printed on the label. VICTRELIS™ can also be stored at room temperature (15°C – 30°C) for up to 3 months. Store in the original container.

Keep VICTRELIS™ and all medicines out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

or at Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at 1-800-567-2594
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-496-9092, or
  - Mail to: Merck Canada Inc.
    Pharmacovigilance
    P.O. Box 1005
    Pointe-Claire - Dorval, QC H9R 4P8

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program or Merck does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Merck Canada Inc. at: 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

Last revised: July 27th, 2011

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