Selected Properties of Boceprevir

Other Names	Victrelis™ Combination formulation: Victrelis Triple™: boceprevir/ribavirin/peginterferon alfa-2b
Manufacturer	Merck
Pharmacology/ Mechanism of action	Equal mixture of two diastereoisomers; the pharmacologically active SCH 534128 (S-isomer) and SCH 534129 (R-isomer). **Mechanism of Action:** Boceprevir is an inhibitor of the HCV NS3/4A protease. Boceprevir 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.
Activity	The IC50 and IC90 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 IC90 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. Boceprevir had approximately 2-fold reduced activity against a genotype 2a isolate relative to genotype 1a and 1b replicon isolates. In a biochemical assay, boceprevir 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 boceprevir and interferon alfa-2b that produced 90 % suppression of replicon RNA showed additivity of effect; no evidence of synergy or antagonism was detected.
Resistance – genotypic	The activity of boceprevir 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 boceprevir anti-HCV activity was conferred by the substitutions: T54C, R155G/I/T and A156S/T/V. The fold decrease in boceprevir anti-HCV activity conferred by double resistance-associated substitutions was approximately equal to the product of that for the individual substitutions.
Resistance - phenotypic	In the pooled resistance analysis from the 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. 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. However, among subjects with a relatively poor response to PegINFα2b/RBV during the 4-week lead-in period, the efficacy of boceprevir appeared to be reduced for those who had V36M, T54A, T54S, V55A or R155K at baseline. 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 boceprevir 800 mg TID in combination with PegIFNα2b/RBV in two Phase 3 studies, post-baseline RAVs were detected in 53 % of non-SVR patients. Interferon responsiveness was associated with detection of fewer RAVs. 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. One or more boceprevir-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. No data are available regarding the efficacy of boceprevir among subjects who were previously exposed to boceprevir, or who previously failed treatment with a boceprevir-containing regimen.
Cross-resistance	Many of the treatment-emergent NS3/4A amino acid substitutions detected in boceprevir-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 boceprevir or treatment failure on the efficacy of other HCV NS3/4A PIs has not been studied. The efficacy of boceprevir has not been established for patients with a history of exposure to other NS3/4A PIs. Cross-resistance is not expected between boceprevir and interferons, or boceprevir and ribavirin.
Oral Bioavailability	Unknown
Effect of Food	Boceprevir must be taken with food. Food enhanced the exposure of boceprevir by up to 60 % at the 800 mg TID dose when administered with a meal, relative to the fasting state. Bioavailability is similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or after a meal.
Protein Binding	75 %
Vd	717 L

Tmax	2 hours
Serum T ½	3 hours
Drug concentrations	In the plasma the diastereoisomer ratio is about 2:1 in favour of the active diastereoisomer, SCH 534128. The plasma concentrations of boceprevir described below consist of both diastereoisomers. In general, PK results were similar between healthy and HCV subjects. AUC, Cmax and Cmin 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. PPK individual prediction from sparse data in HCV patients (boceprevir 800 mg TID): Cmax: 1013 ng/mL Cmin: 213 ng/mL AUC: 4403 ng.hr/mL Population PK estimates HCV patients (boceprevir 800 mg TID): Cmax: 1084 ng/mL Cmin: 218 ng/mL AUC: 4642 ng.hr/mL Healthy subjects (non-compartmental analysis)(boceprevir 800 mg TID): Cmax: 1723 ng/mL Cmin: 88 ng/mL AUC: 5408 ng.hr/mL No gender, race or age-related PK differences have been observed.
Minimum trough concentration (for wildtype virus)	
CSF (% of serum)	Not studied
Metabolism	Boceprevir is metabolized primarily by aldo-ketoreductase (AKR). Boceprevir is partly metabolized by CYP3A4/5. *In vitro,* boceprevir has been shown to be also a substrate of p-glycoprotein.
Excretion	Boceprevir is eliminated primarly by the liver. Following a single 800 mg oral dose of 14C-boceprevir, 79 % and 9 % of the dose was excreted in feces and urine, respectively, with approximately 8 % and 3 % of the dosed eliminated as boceprevir in feces and urine.
Dosing – Adult	**Boceprevir should not be used as monotherapy but only in combination with PegIFNα/RBV.** **It is important that the dose of boceprevir (800 mg) be taken orally TID (every 7-9 hours)** with food (a meal or light snack). Response-Guided Therapy is recommended for most patients, but longer dosing is recommended in target groups (e.g. cirrhosis, prior

	null response). *Consult most up-to-date information for treatment duration and strategies.* **A) Patients without cirrhosis who are previously untreated or who are previous partial responders or relapsers to PegIFNα/RBV therapy:** 1) Initiate therapy with PegIFNα/RBV for 4 weeks (TWs 1-4). 2) Add boceprevir 800 mg (four 200 mg capsules) orally TID (every 7-9 hours) to PegIFNα/RBV regimen at TW 5. Treatment duration is based on whether patients are previously untreated or had previous treatment failures and their HCV-RNA levels at TW 8, TW 12 and TW 24 **B) Patients with prior null response** If considered for treatment, these subjects should receive 4 weeks of PegIFNα/RBV followed by 44 weeks of boceprevir 800mg (four 200 capsules) orally TID (every 7-9 hours) in combination with PegIFNα/RBV **C) Patients without cirrhosis who are previously untreated with a poor interferon response** (less than a 1.0-log10 decline in HCV-RNA at TW 4 with PegIFNα/RBV alone) 4 weeks PegIFNα/RBV followed by 44 weeks of boceprevir 800 mg (four 200 mg capsules) TID (every 7-9 hours) in combination with PegIFNα/RBV **D) Patients with compensated cirrhosis** 4 weeks PegIFNα/RBV followed by 44 weeks boceprevir 800 mg (four 200 capsules) orally TID (every 7-9 hours) in combination with PegIFNα/RBV.
Dosing - Pediatric	No data available
Special instructions for pediatric patients	No data available
Adjust in Liver Dysfunction	No clinically significant differences in PK parameters were found and no dosage adjustment is recommended in patients with mild, moderate or severe hepatic impairment. The PK of a single 400 mg dose of boceprevir under fasted conditions was studied in 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. Mean CL/F values in subjects with moderate and severe hepatic impairment were decreased but remained in the range of healthy subjects. Fasted dosing, a less than therapeutic dose and non-final formulation, limits the generalizability of the conclusions.

	AUC (tf): Mild vs healthy: 107 % (90%CI: 75-152) Moderate vs healthy: 132 % (90%CI: 93-187) Severe vs healthy: 145 % (90%CI: 102-205) Cmax: Mild vs healthy: 115 % (90%CI: 71-188) Moderate vs healthy: 128 % (90%CI: 79-208) Severe vs healthy: 162 % (90%CI: 99-263) Estimates of steady-state maximum AUC and Cmax parameters of patients infected with HCV in the Phase 3 studies were 9,715 ng·h/mL and 2,377 ng/mL, respectively. PegIFNα2b/RBV is contraindicated in the hepatically impaired population. Thus, the use of boceprevir with PegIFNα2b/RBV is also contraindicated in this population.
Adjust in Renal Failure/Dialysis	No dosage adjustment is in patients with any degree of renal impairment. ESRD subjects and matched subjects with normal renal function were administered a single 800 mg dose of boceprevir/ 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 alter PK parameters
Toxicity	*Many of the side effects may be related to PegIFNα2b/RBV* Most common: Anemia (49% when used with PegIFNα2b/RBV) Fatigue, anemia, nausea, headache, and dysgeusia (> 35% when used with PegIFNα2b/RBV) Abdominal pain, constipation, diarrhea, dry mouth, vomiting, GERD Fever, chills, weight loss, decrease appetite, myalgia/arthralgia, dizziness Anxiety, depression, insomnia, irritability, mood alteration Cough, dyspnea Dry skin, pruritus, rash Neutropenia, Thrombocytopenia Blurred vision
Pregnancy & Lactation	Because boceprevir is used in combination with PegIFNα/RBV, it is therefore contraindicated in pregnant women and men whose female partners are pregnant. No studies in pregnant women are available. Pregnancy risk category B (all trimesters). No effects on fetal development have been observed in rats and rabbits with boceprevir exposures 11.8- and 2.0-fold higher, respectively, than those in humans at the recommended dose of 800 TID. Boceprevir has been shown in animals to distribute across the

	placenta to fetal blood and tissues. It is unknown whether boceprevir is excreted into human breast milk. Account the potential for adverse reactions from the drug in nursing infants vs the benefit of therapy for the mother. Available pharmacodynamic/toxicological data in animals have shown excretion of boceprevir and/or metabolites in milk. Consequently a risk to nursing newborns/infants cannot be excluded.
Drug interactions	**Effect of Other Drugs on boceprevir Pharmacokinetics** Boceprevir is partly metabolized by CYP3A4/5. Co-administration with drugs that induce or inhibit CYP3A4/5 could increase or decrease exposure to boceprevir. **Effects of boceprevir on Pharmacokinetics of Other Drugs** Boceprevir is a strong inhibitor of CYP3A4/5. Drugs metabolized primarily by CYP3A4/5 may have increased exposure, which could increase or prolong their therapeutic and adverse effects. *See separate drug interaction chart*. **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).
Baseline assessment	CBC (with WBC differential count) Pregnancy test in female patients and in female partners of male patients
Routine Labs	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. CBC (with WBC differential count) should be obtained 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. Decreases in the neutrophil counts may require dose reduction or discontinuation of PegIFNα/RBV. Monthly pregnancy test in female patients and in female partners of male patients
Dosage Forms	Capsules (Hard-gelatin): 200 mg (yellowish-brown) DIN 02370816

	Peelable aclar/PVC/aluminium blisters containing 12 capsules. 7 blisters per folding carton and 2 folding cartons per outer carton Combination formulations: Boceprevir 200 mg capsules plus Ribavirin 200 mg capsules plus peginterferon alfa-2b powder for solution in REDIPEN® single dose delivery system DIN: 02371448; 02371456; 02371464; 02371472 **Deliverable Dose 80 mcg/0.5 mL** A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 28 RBV capsules each for a total of 56 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 80 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders. **Deliverable Dose 100 mcg/0.5 mL** A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 28 RBV capsules each for a total of 56 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 100 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders. **Deliverable Dose 120 mcg/0.5 mL** A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 35 RBV capsules each for a total of 70 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 120 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders. **Deliverable Dose 150 mcg/0.5 mL** 1. A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 42 RBV capsules each for a total of 84 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 150 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders. 2. A carton containing two boxes of 84 BOC capsules each for a total of 168 BOC capsules, two boxes of 49 RBV capsules each for a total of 98 RBV capsules, plus two PegIFNα2b REDIPEN® single dose delivery systems, 150 mcg/REDIPEN®, with two 30-gauge needles (0.3 x 8 mm), 4 alcohol swabs and two pen holders.
Storage	Boceprevir capsules should be refrigerated at 2^{o}C – 8^{o}C. Can also be stored at room temperature (15℃ – 30℃) for up to 3 months. Store in the original container.

References

Victrelis™. Product Monograph. Merck Canada Inc, Kirkland, Quebec, Canada, July 2011.