



February 6, 2012

**IMPORTANT DRUG WARNING**

**SUBJECT: Results of Pharmacokinetic Study in Healthy Volunteers Given VICTRELIS™ (boceprevir) and Ritonavir-Boosted HIV Protease Inhibitors May Indicate Clinically Significant Drug Interactions for Patients Coinfected with Chronic Hepatitis C and HIV**

Dear Health Care Professional,

The purpose of this communication is to inform you of recent pharmacokinetic study results evaluating drug interactions between VICTRELIS, an oral chronic hepatitis C virus (HCV) NS3/4A protease inhibitor, and ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitors in healthy volunteers (n=39). VICTRELIS is indicated for the treatment of chronic hepatitis C virus (HCV) genotype 1 (G1) infection, in combination with peginterferon alfa and ribavirin (PR), in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are treatment-naïve or who have failed previous interferon and ribavirin therapy. In the pharmacokinetic study, concomitant administration of VICTRELIS with *Norvir*® (ritonavir) in combination with *Reyataz*® (atazanavir) or *Prezista*® (darunavir), or with *Kaletra*® (lopinavir/ritonavir) resulted in reduced exposures of the HIV medicines and VICTRELIS. Specifically, VICTRELIS reduced mean trough concentrations of ritonavir-boosted atazanavir, lopinavir, and darunavir by 49%, 43%, and 59%, respectively. Mean reductions of 34% to 44% and 25% to 36% were observed in AUC and C<sub>max</sub> of atazanavir, lopinavir, and darunavir. Coadministration of ritonavir-boosted atazanavir with VICTRELIS did not alter the exposure of VICTRELIS, but coadministration of VICTRELIS with lopinavir/ritonavir or ritonavir-boosted darunavir decreased the exposure of VICTRELIS by 45% and 32%, respectively.

These drug interactions may be clinically significant for patients infected with both chronic HCV and HIV by potentially reducing the effectiveness of these medicines when coadministered. VICTRELIS is not indicated for use in patients who are infected with both HIV-1 and chronic HCV. The safety and efficacy of VICTRELIS™ (boceprevir) has not been established in this coinfecting population. Merck does not recommend the coadministration of VICTRELIS and ritonavir-boosted HIV protease inhibitors.

Health care providers who might have initiated VICTRELIS in combination with PR in HIV-HCV coinfecting patients on fully suppressive antiretroviral therapy containing a ritonavir-boosted protease inhibitor should discuss these findings with those patients, and closely monitor those patients for HCV treatment response and for potential HCV and HIV virologic rebound.

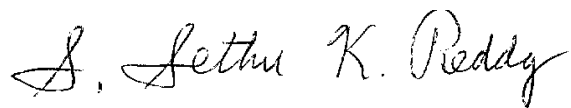
**Patients should be advised to contact their health care provider before stopping any of their medications.**

Merck is sharing these pharmacokinetic data with regulatory authorities in the countries where VICTRELIS is approved. Merck will be submitting requests to regulators to update the product labeling with these data. These data have been submitted for scientific presentation at an upcoming medical forum.

For more information, please consult the enclosed Prescribing Information for VICTRELIS. The Prescribing Information can also be found at [http://www.merck.com/product/usa/pi\\_circulars/v/victrelis/victrelis\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf).

Should you have any questions, require further information on product safety, or wish to report an adverse event with VICTRELIS, please contact Merck at 1-877-888-4231. Alternatively, an adverse event can be reported directly to the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Sincerely,

A handwritten signature in black ink that reads "S. Sethu K. Reddy". The signature is written in a cursive, flowing style.

S. Sethu K. Reddy, MD

Enclosure: Prescribing Information for VICTRELIS

## Indications and Usage for VICTRELIS™ (boceprevir)

VICTRELIS was approved by the US Food and Drug Administration (FDA) on May 13, 2011 for the treatment of chronic hepatitis C virus (HCV) genotype 1 (G1) infection, in combination with peginterferon alfa and ribavirin (PR), in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

The following points should be considered when initiating VICTRELIS for treatment of chronic HCV infection:

- VICTRELIS must not be used as monotherapy and should only be used in combination with PR.
- VICTRELIS efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes VICTRELIS or other HCV NS3/4A protease inhibitors.
- VICTRELIS in combination with PR has not been studied in patients documented to be historical null responders ( $<2\text{-log}_{10}$  HCV-RNA decline by Treatment Week 12) during prior therapy with PR. The clinical studies included subjects who were poorly interferon responsive. Subjects with  $<0.5\text{-log}_{10}$  HCV-RNA decline in viral load at Treatment Week 4 with PR alone are predicted to have a null response ( $<2\text{-log}_{10}$  viral load decline at Treatment Week 12) to PR therapy.
- Poorly interferon responsive patients who were treated with VICTRELIS in combination with PR have a lower likelihood of achieving a sustained virologic response (SVR), and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to PR.

## Selected Safety Information for VICTRELIS

All contraindications to PR also apply since VICTRELIS must be administered with PR.

Because ribavirin may cause birth defects and fetal death, VICTRELIS in combination with PR is contraindicated in pregnant women and in men whose female partners are pregnant. Avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to therapy; have monthly pregnancy tests; and use 2 or more forms of effective contraception, including intrauterine devices and barrier methods, during treatment and for at least 6 months after treatment has concluded. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS and concomitant ribavirin.

VICTRELIS is contraindicated in coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. VICTRELIS is also contraindicated in coadministration with potent CYP3A4/5 inducers, where significantly reduced VICTRELIS plasma concentrations may be associated with reduced efficacy.

Drugs that are contraindicated with VICTRELIS include: alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort (*hypericum perforatum*), lovastatin, simvastatin, drospirenone, *Revatio*® (sildenafil) or *Adcirca*® (tadalafil) (when used for the treatment of pulmonary arterial hypertension), pimozide, triazolam, and orally administered midazolam.

Anemia and/or Neutropenia – The addition of VICTRELIS™ (boceprevir) to PR is associated with an additional decrease in hemoglobin concentrations compared with PR alone and/or may result in worsening of neutropenia associated with PR therapy alone. Dose reduction or discontinuation of peginterferon alfa and/or ribavirin may be required. Dose reduction of VICTRELIS is not recommended. VICTRELIS must not be administered in the absence of PR.

Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating combination therapy with VICTRELIS. Complete blood counts should be obtained at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate.

The most commonly reported adverse reactions (>35%) in clinical trials in adult patients receiving the combination of VICTRELIS with PR were: fatigue, anemia, nausea, headache, and dysgeusia. Of these commonly reported adverse reactions, fatigue, anemia, nausea, and dysgeusia occurred at rates  $\geq 5\%$  above the rates for PR alone in either clinical study. The incidence of these adverse reactions in previously untreated subjects that were treated with combination therapy with VICTRELIS compared with PR alone were: fatigue (58% vs 59%), anemia (50% vs 30%), nausea (46% vs 42%), and dysgeusia (35% vs 16%), respectively. The incidence of these adverse reactions in previous treatment failure patients that were treated with combination therapy with VICTRELIS compared with PR alone were: fatigue (55% vs 50%), anemia (45% vs 20%), nausea (43% vs 38%), and dysgeusia (44% vs 11%), respectively.

VICTRELIS is a strong inhibitor of CYP3A4/5 and is partly metabolized by CYP3A4/5. The potential for drug-drug interactions must be considered prior to and during therapy.

Other products mentioned are the trademarks of their respective owners and are not trademarks of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Copyright © Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. All rights reserved.

INFC-1025723-0000