

August 11, 2014

**Subject: Discontinuation of INCIVEK® (telaprevir) tablets in the United States**

Dear Healthcare Provider:

The purpose of this letter is to inform you that Vertex Pharmaceuticals Incorporated will be discontinuing the sale and distribution of INCIVEK in the United States by October 16<sup>th</sup>, 2014. INCIVEK is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic HCV in adult patients with compensated liver disease. The complete indication for INCIVEK is located at the end of this letter.

This decision has been taken in view of available alternative treatments and the diminishing market demand for INCIVEK.

We request that healthcare providers not start any new patients on INCIVEK at this time because of the discontinuation of the sale and distribution of INCIVEK. Vertex will continue to provide financial support to eligible patients currently prescribed INCIVEK and, for those currently under treatment, will address available drug supply needs to complete treatment regimen. For INCIVEK product support information, please contact: 1-877-824-4281.

Enclosed you will find the complete US Prescribing Information, including Boxed Warning, and Medication Guide.

Should you have any questions, require further information, or wish to report adverse patient experiences associated with the use of INCIVEK, please call

- Vertex Medical Information at 1-877-824-4281.
- Alternatively, report this information to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online ([www.accessdata.fda.gov/scripts/medwatch](http://www.accessdata.fda.gov/scripts/medwatch)) or by mail via the MedWatch Form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

The complete indication for INCIVEK:

INCIVEK (telaprevir), in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.

The following points should be considered when initiating treatment with INCIVEK:

- INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin.
- A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with INCIVEK combination treatment.
- INCIVEK efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes INCIVEK or other HCV NS3/4A protease inhibitors.

## Important safety information:

### WARNING: SERIOUS SKIN REACTIONS

- **Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with INCIVEK (telaprevir) combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive INCIVEK combination treatment after a serious skin reaction was identified**
- **For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, INCIVEK, peginterferon alfa, and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care**

### Contraindications

- INCIVEK combination treatment is contraindicated in women who are or may become pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. If ribavirin is used during pregnancy or in the event of a pregnancy while on treatment, inform the patient of the potential hazard to a fetus. INCIVEK combination treatment is also contraindicated in men whose female partners are pregnant
- INCIVEK is a strong inhibitor of CYP3A. INCIVEK is contraindicated when combined with drugs that 1) are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events and 2) strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of INCIVEK. Contraindicated medications are alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's wort, lovastatin, simvastatin, pimozide, sildenafil (Revatio<sup>®</sup>) or tadalafil (Adcirca<sup>®</sup>) for pulmonary arterial hypertension, oral midazolam, and/or triazolam

### Warnings and precautions

- See Boxed Warning regarding serious skin reactions at beginning of Important Safety Information
- In clinical trials, serious skin reactions, including DRESS and SJS were reported in <1% of subjects who received INCIVEK combination treatment compared to none who received peginterferon alfa and ribavirin alone. These serious skin reactions required hospitalization, and all subjects recovered. Presenting signs of these reactions may include rash, fever, facial edema, target lesions, mucosal ulcerations, and evidence of internal organ involvement
- TEN and Erythema Multiforme (EM) have been observed in post-marketing experience
- Rash events (all grades) developed in 56% of patients who received INCIVEK combination treatment compared to 34% with peginterferon alfa and ribavirin alone. Severe rash was reported in 4% of patients treated with INCIVEK combination treatment compared to <1% with peginterferon alfa and ribavirin alone. Severe rash may have a prominent eczematous component. Patients with mild to moderate rash should be followed for progression of rash or development of systemic symptoms. If rash becomes severe, discontinue INCIVEK. Peginterferon alfa and ribavirin may be continued. If improvement is not observed within 7 days of discontinuing INCIVEK, consider sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa; earlier interruption or discontinuation may be medically indicated. Monitor patients until the rash has resolved. INCIVEK must not be reduced or restarted if discontinued due to rash. Treatment of rash with systemic corticosteroids is not recommended

## Important safety information (continued):

- Anemia has been reported with peginterferon alfa and ribavirin treatment. Adding INCIVEK (telaprevir) is associated with an additional decrease in hemoglobin compared to peginterferon alfa and ribavirin alone. Hemoglobin values of  $\leq 10$  g per dL were observed in 36% of patients, and  $< 8.5$  g per dL in 14% of patients who received INCIVEK combination treatment compared to 17% and 5%, respectively, with peginterferon alfa and ribavirin alone
- Hemoglobin should be monitored prior to and at least at weeks 2, 4, 8, and 12 during INCIVEK combination treatment and as clinically appropriate. Earlier and more frequent monitoring for some patients should be considered. Use the labeled ribavirin dose modification guidelines to manage anemia; if ribavirin dose reductions are inadequate, consider discontinuing INCIVEK. If ribavirin is permanently discontinued, INCIVEK must also be permanently discontinued. The dose of INCIVEK must not be reduced and must not be restarted if discontinued
- Pregnancy: Ribavirin may cause defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained just before initiation of therapy
- Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during combination treatment and for 6 months after all treatment has ended. Female patients should have monthly pregnancy tests during treatment and during the 6-month period after stopping all treatment. Female patients may continue hormonal contraceptives but they may not be reliable during INCIVEK dosing and for up to 2 weeks after stopping INCIVEK. During this time, female patients of childbearing potential should use 2 effective non-hormonal methods of contraception
- A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes in patients exposed to ribavirin
- Monitor HCV RNA levels at Weeks 4 and 12 and as clinically indicated. Hematology evaluations are recommended prior to and at weeks 2, 4, 8, and 12, and as clinically appropriate. Chemistry evaluations are recommended as frequently as hematology evaluations or as clinically appropriate

### Adverse reactions

- The most common adverse reactions seen with an incidence  $\geq 5\%$  with INCIVEK over controls were rash, fatigue, pruritus, nausea, anemia, diarrhea, vomiting, hemorrhoids, anorectal discomfort, dysgeusia, and anal pruritus

Contraindications, Warnings and Precautions, and Adverse Reactions to peginterferon alfa and ribavirin also apply to INCIVEK combination treatment.

Thank you for your attention to this matter.

Sincerely,



Charles Johnson, MD  
Vice President, Global Medical Affairs