



Investigation results

simeprevir sodium

October 24, 2014

Product information

Brand Name (Marketing Authorization Holder)

SOVRIAD Capsules 100 mg (Janssen Pharmaceuticals K.K.)

Non-proprietary Name

Simeprevir sodium

Indications

Improvement of viraemia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection:

- (1) Treatment-naïve patients with high blood HCV RNA load
- (2) Patients who have failed to respond to, or have relapsed after, therapy including interferon

The estimated number of patients using simeprevir sodium

Approximately 18,900 (from the launch on December 6, 2013 to September 30, 2014)

Summary

Simeprevir sodium is used for the treatment of chronic hepatitis C as a combination therapy with peginterferon and ribavirin.

In clinical trials in Japan, the incidence proportion of increased blood bilirubin-associated events was 31.5% (104/330 cases) in the simeprevir group and 8.2% (6/73 cases) in the placebo group. Inhibition of hepatic transporters (organic anion transporting polypeptide 1B1 and multidrug resistance-associated protein 2) by simeprevir may mainly contribute to the increased blood bilirubin levels in patients treated with simeprevir. Although the incidence proportion of increased blood bilirubin-associated events was relatively high in the trial in Japan, most of the events were mild and the patients recovered after completion or discontinuation of simeprevir.



On the basis of a review of such available evidence, the MHLW/PMDA considered that combination therapy including simeprevir can be beneficial while paying careful attention to blood bilirubin levels during the treatment course. In order to raise caution, it has been required to monitor blood bilirubin levels during treatment under the section of “Important Precautions” of the package insert since the launch of simeprevir. The package insert has also included information on increased blood bilirubin and hyperbilirubinaemia in the section of “Other Adverse Reactions.”

A total of 8 cases of remarkably increased blood bilirubin* have been reported in patients treated with the combination therapy including simeprevir in post-marketing surveillance (including 7 cases in which causality could not be ruled out). Of the 8 cases, 3 fatalities have been reported and causality could not be ruled out in all 3 cases. Following investigation results based on opinions of expert advisors and available evidence, the MHLW/PMDA concluded that revision of the package insert of simeprevir was necessary.

Regarding hepatic dysfunction, the current package insert does not include an alert against the relevant hepatic events. A total of 15 cases of serious hepatic dysfunction-associated events** have been reported in patients treated with the combination therapy including simeprevir (including 12 cases in which causality could not be ruled out). Of the 15 cases, 3 fatalities have been reported and causality could not be ruled out in all 3 cases (the 3 fatalities are identical with the aforementioned 3 cases of remarkably increased blood bilirubin levels in the previous paragraph). Following investigation results based on opinions of expert advisors and available evidence, the MHLW/PMDA concluded that revision of the package insert of simeprevir was necessary.

*cases of ≥ 10 mg/dL of blood bilirubin levels

**cases of ≥ 500 IU/mL of AST (aspartate aminotransferase) or ALT (alanine aminotransferase), including cases with unknown clinical laboratory values.

Evaluation Results

Following an investigation based on opinions of expert advisors and available evidence, the PMDA concluded that the revision of Precautions should be implemented in an urgent manner due to the following reasons:



This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

- Although increased blood bilirubin levels associated with simeprevir are already known, 3 cases of remarkably increased blood bilirubin levels leading to fatalities have been reported over a short period of 10 months after the sales launch and the causality could not be ruled out in all 3 cases.
- The review of an association between increased blood bilirubin levels and fatalities showed that the deaths occurred after hepatic dysfunction and renal impairment in the 3 fatal cases. Therefore, hyperbilirubinaemia may contribute to hepatic dysfunction and renal impairment.
- In all 3 fatal cases, blood bilirubin levels surged following persistent increase after administration of simeprevir had started. Further increases of blood bilirubin were noted even after discontinuation of simeprevir. Therefore, blood bilirubin tests should be performed regularly during the treatment courses with simeprevir, and patients should be carefully monitored even after discontinuation of simeprevir. Once jaundice, general malaise, and/or other symptoms occur, measure may be less effective to avoid serious outcomes.

Based on the above reasons, the MHLW/PMDA concluded that the marketing authorization holder, in collaboration with the MHLW/PMDA, should fully inform healthcare professionals and patients of fatal cases associated with remarkably increased blood bilirubin and appropriate safety measures to avoid serious outcomes.



This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Appendix

Proposed Revisions of PRECAUTIONS in the Package Insert

Revised	Current
<p>Warnings</p> <ol style="list-style-type: none"> This drug must be administered under supervision of a physician with sufficient knowledge and experience in the treatment of viral liver disease only to patients in whom treatment with this drug is deemed appropriate. <u>Cases of remarkable increase in blood bilirubin levels followed by hepatic dysfunction and/or renal impairment, etc. leading to death have been reported in patients treated with this drug. Pay attention to the followings:</u> <ol style="list-style-type: none"> <u>Blood bilirubin tests should be performed regularly during the treatment course with this drug.</u> <u>If any abnormalities are observed including persistent increase in blood bilirubin levels, administration of this drug should be discontinued and appropriate measures should be taken.</u> <u>Blood bilirubin levels may be increased even after discontinuation of this drug. Therefore the patients' condition should be carefully observed.</u> <u>Patients should be advised to see their doctor immediately when colouring yellow of ocular and/or skin, brown urine, and/or general malaise, etc. are observed after the treatment courses.</u> 	<p>Warnings</p> <p>This drug must be administered under the supervision of a physician with sufficient knowledge and that experience in the treatment of viral liver disease only to patients in whom treatment with this drug is deemed appropriate.</p>
<p>Precautions for Indications</p> <p>Prior to initiate the administration of this drug to patients, healthcare professionals should check that blood hepatitis C virus –ribonucleic acid is positive and that <u>hepatic cirrhosis is ruled out</u> based on histology, residual function of the liver, platelet count, etc.</p>	<p>Precautions for Indications</p> <p>Prior to initiate the administration of this drug to patients, healthcare professionals should check that blood hepatitis C virus-ribonucleic acid is positive. and that chronic hepatitis is diagnosed based on histology, residual function of the liver, platelet count, etc.</p>



This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

<p>Precautions</p> <p>2. Important Precautions</p> <p>No related information</p>	<p>Precautions</p> <p>2. Important Precautions</p> <p>(2) Increased blood bilirubin levels have been reported in the treatment with this drug. Blood bilirubin levels, liver function test values and/or patients' condition should be carefully monitored during the treatment courses with this drug. If hepatic function is aggravated, administration of this drug should be discontinued and appropriate measures should be taken.</p>
<p>4. Adverse reactions</p> <p>(1) Clinically significant adverse reactions</p> <p><u>Hyperbilirubinaemia (incidence unknown)</u></p> <p><u>Blood bilirubin levels may be remarkably increased. Cases of remarkable increase in blood bilirubin levels followed by hepatic dysfunction and/or renal impairment, etc. leading to death have been reported. Blood bilirubin tests should be performed regularly during the treatment courses with this drug. Patients' condition should be carefully observed. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. (See Warnings section)</u></p> <p><u>Hepatic dysfunction (incidence unknown)</u></p> <p><u>Hepatic dysfunction accompanied by increased aspartate aminotransferase (glutamate oxaloacetate transaminase), alanine aminotransferase (glutamate pyruvate transaminase), alkaline phosphatase, gamma-glutamyl transpeptidase, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.</u></p>	<p>4. Adverse reactions</p> <p>(1) Clinically significant adverse reactions</p> <p>No related information</p>

————— : revision, ===== : deletion