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

Summary of investigation results

Sofosbuvir, Ribavirin, Ledipasvir acetonate/Sofosbuvir

Non-proprietary name

(1) Sofosbuvir
(2) Ribavirin
(3) Ledipasvir acetonate / Sofosbuvir

Brand name (Marketing authorization holder)

(1) Sovaldi Tablets 400 mg (Gilead Sciences K.K.)
(2) Rebetol Capsules 200 mg (MSD K.K.), Copegus 200 mg (Chugai Pharmaceutical Co., Ltd.)
(3) Harvoni Combination Tablets (Gilead Sciences K.K.)

Indications

Refer to the attachment below.

Summary of revision

(1)

1. “Hypertension” should be newly added to the Clinically significant adverse reaction section.
2. “Cerebrovascular disorder” should be newly added to the Clinically significant adverse reaction section.

(2)

1. “Hypertension” should be newly added to the <Concomitant use with sofosbuvir> subsection in the Clinically significant adverse reaction section.
2. “Cerebrovascular disorder” should be newly added to the <Concomitant use with sofosbuvir> subsection in the Clinically significant adverse reaction section.

(3)

1. The Clinically significant adverse reaction subsection should be newly added to the Adverse reaction section in the package insert. In this new Clinically significant

adverse reaction subsection, “hypertension” should be added.

2. The Clinically significant adverse reaction subsection should be newly added to the Adverse reaction section in the package insert. In this new Clinically significant adverse reaction subsection, “cerebrovascular disorder” should be added.

Background of the revision and investigation results

Cases of severe hypertension in patients concomitantly administered sofosbuvir and ribavirin and in patients administered the combination product of ledipasvir acetonate/sofosbuvir have been reported in Japan. Following an investigation result based on the opinions of expert advisors and the available evidence, the MHLW/PMDA concluded that “Hypertension” should be added in the Clinically significant adverse reaction subsection. A case of severe hypertension resulting in cerebral haemorrhage has also been reported with the combination product of ledipasvir acetonate/sofosbuvir. The MHLW/PMDA discussed whether alerts regarding cerebrovascular disorders were required in the package insert. Cases of cerebrovascular disorders such as cerebral haemorrhage or cerebral infarction associated with concomitant administration of sofosbuvir and ribavirin as well as with administration of the combination product of ledipasvir acetonate/sofosbuvir have been reported in Japan. Following an investigation result based on the opinions of expert advisors and the available evidence, the MHLW/PMDA concluded that “Cerebrovascular disorder” should be added in the Clinically significant adverse reaction subsection separately from “Hypertension” because a causal relationship between cerebrovascular disorder and hypertension was unclear.

The number of reported adverse reactions and fatal cases in the last three fiscal years in Japan

1. “Hypertension” *

(1)(2)

A case † of hypertension has been reported (the causal relationship to the product could not be ruled out for this case). No fatality has been reported.

(3)

A total of 7 cases of hypertension have been reported (including 5 cases for which a causal relationship to the product could not be ruled out). No fatality has been reported.

2. “Cerebrovascular disorder”

(1)(2)

A total of 25 cases[†] of cerebrovascular disorder have been reported (including 8 cases for which a causal relationship to the product could not been ruled out). Of the 25 cases, 2 fatalities have been reported (the causal relationship between the product and the fatal outcome could not be established for these cases).

(3)

A total of 30 cases of cerebrovascular disorder have been reported (including 11 cases for which a causal relationship to the product could not be ruled out). Of the 30 cases, 3 fatalities have been reported (the causal relationship between product and the fatal outcome could not be established for these cases).

[*] Cases in which systolic blood pressure greater than or equal to 180 mmHg or diastolic blood pressure greater than or equal to 110 mmHg.

[†] Cases with concomitant administration of sofosbuvir and ribavirin

Pharmaceuticals and Medical Devices Agency
Office of Safety I
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

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

Attachment

Brand name	**Indications**
Sovaldi Tablets 400 mg	Improvement of viremia in patients with serogroup 2 (genotype 2) chronic hepatitis C virus infection or compensated cirrhosis C
Rebetol Capsules 200 mg	1. Improvement of viremia when used concomitantly with interferon alfa-2b (genetical recombination), peginterferon alfa-2b (genetical recombination), or interferon beta in any of the following patients with chronic hepatitis C virus infection: (1) Patients with high blood HCV RNA load (2) Patients who have failed to respond to, or have relapsed after, interferon monotherapy 2. Improvement of viremia when used concomitantly with peginterferon alfa-2b (genetical recombination) in patients with compensated cirrhosis C 3. Improvement of viremia when used concomitantly with sofosbuvir in patients with serogroup 2 (genotype 2) chronic hepatitis C virus infection or compensated cirrhosis C
Copegus 200 mg	1. Improvement of viremia when used concomitantly with interferon alfa-2a (genetical recombination) in any of the following patients with chronic hepatitis C virus infection: (1) Serogroup 1 (genotype I [1a] or II [1b]) patients with high HCV RNA loads (2) Patients who have failed to respond to, or have relapsed after, interferon monotherapy 2. Improvement of viremia when used concomitantly with peginterferon alfa-2a (genetical recombination) in patients with compensated cirrhosis C 3. Improvement of viremia when used concomitantly with sofosbuvir in patients with serogroup 2 (genotype 2) chronic hepatitis C virus infection or compensated cirrhosis C
Harvoni Combination Tablets	Improvement of viremia in patients with serogroup 1 (genotype 1) chronic hepatitis C virus infection or compensated cirrhosis C

Pharmaceuticals and Medical Devices Agency
Office of Safety I
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp