Simeprevir Sodium and Hyperbilirubinaemia

Details of 3 cases of hyperbilirubinaemia with use of simeprevir sodium are shown below.
(This information has been posted on the website prior to the publication of the English full text of the Pharmaceuticals and Medical Devices Safety Information No. 318)

Case 1

Patient		Daily dose/ Treatment duration	Adverse reactions	
Gender/ Age	Reason for Use (complications)		Clinical course and Treatment	
Male 40s	Chronic hepatitis C (unknown)	100 mg /67 days	History of hyperlipidemia. No history of hepatic impairment, no complication of biliary tract disease, no previous treatment, and no history of alcohol consumption.	
			Approx. 5 years before administration	Chronic hepatitis C was diagnosed.
			44 days before administration	Hepatitis C virus-ribonucleic acid (HCV-RNA) was 5.70 log IU/mL (detected by real-time polymerase chain reaction).
			32 days before administration	Chronic hepatitis and fatty liver were detected by echography. No splenomegaly and ascites were found. Started to administrate rosuvastatin calcium.
			12 days before administration	Platelet count was 9.0 X 10^4/mm^3
			1 day before administration	Liver biopsy:A1F2
			Day 1 of administration:	Three drugs of combination therapy with simeprevir sodium (100mg/day), peginterferon alfa-2b (120 μg/week), and ribavirin (800mg/day) was started. There were no appreciable clinical symptoms such as jaundice when this three drugs of combination therapy was started.
			Date unknown:	Hyperthyroidism occurred.
			Day 21 of administration	Started to administrate olopatadine hydrochloride. (date unknown for discontinuation)
			Day 42 of administration	Rosuvastatin calcium was discontinued.
			Day 56 of administration	Total bilirubin: 3.3 mg/dL.
			Day 63 of administration	General malaise occurred, no blood test. Administration of peginterferon alfa-2b was discontinued.
			Day 67 of administration (day of discontinuation)	The patient felt anorexia and stopped to administrate simeprevir sodium and ribavirin by himself.
			3 days after discontinuation (10 weeks after combination therapy started)	The patient visited a hospital with general malaise. He was admitted to hospital on this day because laboratory tests showed increased in total bilirubin of 25.7 mg/dL. Hyperbilirubinaemia occurred. Computed tomography (CT) showed no biliary obstruction but revealed ascites. Other findings included gallbladder enlargement, and hepatic cirrhosis. Hepatic B virus (HBV) test result was negative
			4 days after discontinuation	All of the test results of hepatitis A virus (HAV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), antinuclear antibody, antimitochondrial antibody, and smooth muscle antibody were negative.
			7 days after discontinuation	Drug lymphocyte stimulation tests (DLST) showed negative for simeprevir sodium, peginterferon alfa-2b, and olopatadine hydrochloride and positive for ribavirin. The stimulation index (SI) for ribavirin was the highest, and the SI for simeprevir sodium was the second highest. Methylprednisolone sodium succinate 1 g/day was administered from this day for 9 days after discontinuation of simeprevir sodium. The patient did not respond to steroid pulse therapy.
			10 days after discontinuation	Left-hand finger cellulitis developed. Antibiotic cefazolin sodium was administered from this day through 19 days after discontinuation of simeprevir sodium. Methylprednisolone sodium succinate 80 mg/day was administered from this day for 15 days after discontinuation of simeprevir sodium.
			15 days after discontinuation	CT scan showed hepatic atrophy, increased ascites, increased levels of mesenteric adipose tissue, gallbladder atrophy, and gallbladder wall thickening. Serious hepatitis was diagnosed (Hepatitis fulminant was suspected).
			16 days after discontinuation	Methylprednisolone sodium succinate 60 mg/day was administered from this day for 17 days after discontinuation of simeprevir sodium.

Patient		Daily dose/ Treatment duration	Adverse reactions	
Gender/ Age	Reason for Use (complications)		Clinical course and Treatment	
			18 days after discontinuation	Hepatic failure occurred. The cause of hepatic failure: drug-induced hepatic impairment. The clinical symptoms of hepatic failure were jaundice, fatigue, disorientation or confusion, encephalopathy, and ascites. Artificial ventilation, haemodialysis, steroid pulse therapy, and plasmapheresis were conducted as ancillary therapy. Prothrombin time activity was below 40%. The patient experienced disturbed consciousness and decreased blood pressure. The tranquilizer was administered to the patient due to rampage and naked. It was unknown that the disturbed consciousness was associated with sepsis or hepatic encephalopathy Ammonia: 36μg/dL. Then the patient moved to the ICU and liver transplantation was considered but denied by the patient.
			19 days after discontinuation	Aspartate aminotransferase (AST): 2 300 IU/L. Total bilirubin (T-Bil): 26.8 mg/dL. Disturbed consciousness, severe jaundice, hepatocellular necrosis were noted. HCV-RNA was not detected.
			20 days after discontinuation	Culture (Blood culture from artery) revealed that the pathogen was *Serratia marcescens*. Bacterial sepsis was diagnosed. Clinical findings were shock, hepatic failure, and disseminate intravascular coagulation.
			21 days after discontinuation	T-Bil: 20.2mg/dL The patient died of bacterial sepsis, hepatic failure, serious hepatitis (suspected hepatitis fulminant), hepatic cirrhosis, and peritonitis. The condition of the patient's liver was changed compared to that before administration of simeprevir sodium, and resulted in hepatic failure. The causes of death were bacterial sepsis resulting from immunological deterioration, hepatic failure, and peritonitis. The autopsy showed hepatic cirrhosis, hepatocellular necrosis, peritonitis, and acute pancreatitis.
Concomitant drugs: peginterferon alfa-2b, ribavirin, rosuvastatin calcium, olopatadine hydrochloride				

Laboratory Examination

	12 days before administration	Day 1 of administration	Day 7 of administration	Day 14 of administration	Day 28 of administration	Day 35 of administration	Day 42 of administration
Plt($\times10^4$/mm^3)	9.0	8.3	6.7	6.7	4.8	6.6	6.8
PT (%)	77.0	95.0	103.0	103.0	100.0	98.0	103.0
Alb(g/dL)	4.2	3.9	4.1	3.8	3.8	3.8	4.0
T-Bil(mg/dL)	1.4	1.0	1.7	1.1	1.8	1.9	2.5
D-Bil(mg/dL)	0.2	－	－	0.2	0.5	0.7	0.9
AST(IU/L)	72	63	48	41	49	58	85
ALT(IU/L)	120	95	76	54	57	75	103
ALP(IU/L)	248	236	229	253	294	300	325
γ-GTP(IU/L)	39	34	39	34	36	36	42
WBC(/mm^3)	6,200	6,900	5,100	3,700	3,900	5,500	5,900

	Day 49 of administration	Day 56 of administration	3 days after discontinuation	10 days after discontinuation	15 days after discontinuation	19 days after discontinuation	21 days after discontinuation
Plt($\times10^4$/mm^3)	7.4	6.1	6.2	11.6	8.3	3.5	1.3
PT (%)	116	131.0	95.0	95.0	72.0	34.0	19.0
Alb(g/dL)	3.7	3.5	2.9	3.3	3.1	2.6	2.5
T-Bil(mg/dL)	3.0	3.3	25.7	37.2	44.1	26.8	20.2
D-Bil(mg/dL)	1.3	1.9	16.7	24.5	34.5	18.3	13.0
AST(IU/L)	68	56	80	52	59	2300	557
ALT(IU/L)	79	59	51	46	39	1028	320
ALP(IU/L)	335	324	431	505	515	245	284
γ-GTP(IU/L)	45	48	32	27	24	17	21
WBC(/mm^3)	4,900	4,300	5,200	12,800	20,800	23,800	3,500

－ : No data

Case2

Patient		Daily Dose/ Treatment duration	Adverse reactions	
Gender/ Age	Reason for Use (Complications)		Clinical course and Treatment	
Male 60s	Chronic hepatitis C (Hepatic cirrhosis, Type 2 diabetes mellitus and duodenal ulcer)	100 mg /84 days	BW: approx. 70 kg, Height: approx. 160 cm, rugged. Negative to attend to the hospital. No history of Chronic hepatitis C therapy. No history of allergy, no diabetic nephropathy, no history of alcohol consumption.	
			28 days before administration	CT scan showed hepatic cirrhosis, no enlargement of biliary tract. No punctuate (ascites/liver) conducted. Plt: 8.5 X 10^4 /mm^3 T-Bil: 1.5 mg/dL
			Day 1 of administration :	Three drugs of combination therapy with simeprevir (100 mg/day), peginterferon alfa-2a (45 μg/week), and ribavirin (800 mg/day) was started in another hospital. There was no clinical symptoms associated with liver cirrhosis when three combination therapy was started. The patient had mild but clinically-insignificant diabetes mellitus. At the initiation of administration, WBC was 12 100/mm^3, however, no symptoms.
			Day 57 of administration	T-Bil: 4.0 mg/dL. Creatinin: 0.96 mg/dL.
			Day 72 of administration	Creatinine: 0.88 mg/dL.（No data available from this day to 15 days after discontinuation of simeprevir sodium.)
			Approx. Day 80 of administration	Abnormalities had not been specified before this day. However, general malaise, anorexia, and weight loss (decreased by 7 kg in 3 weeks to 63 kg) were noted. The urine output also began to decrease.
			Day 84 of administration (day of completion)	Administration of simeprevir sodium was completed.
			15 days after completion	Because the patient condition was bad, decreased dose of peginterferon alfa-2a (22.5 μg/week), then discontinued and followed up. No data of bilirubin.
			22 days after completion	Drug-induced cholestatic hepatic disorder and acute renal failure developed. Creatinine and total bilirubin were increased, and cholestasis and acute renal failure concurrently developed. Because advanced cholestatic liver disorder was considered to have induced acute renal failure, intensive care such as plasmapheresis, haemodiafiltration, and steroid pulse therapy was performed. However, the patient did not respond to intensive care. Diagnostic imaging showed no biliary dilatation The clinical signs and symptoms associated with drug-induced cholestatic hepatic disorder included jaundice, fatigue, nausea, malaise, anorexia, and renal failure. The clinical signs and symptoms associated with acute renal failure included oliguria, general malaise, impaired appetite and disturbed consciousness.
			25 days after completion	Creatinine: 1.70 mg/dL
			53 days after completion	There was no improvement in the laboratory data after 3 weeks of admission to the hospital. The patient did not want to continue haemodialysis. In the afternoon, the patient died of multi-organ failure. Causes of death were drug-induced cholestatic hepatic disorder, renal failure acute, and multi-organ failure. Autopsy was not performed Plasmapheresis, haemodiafiltration, and steroid pulse therapy were performed before death. DLST: positive for simeprevir
Concomitant drugs: rivabirin, peginterferon alfa-2a, loxoprofen sodium hydrate, and fexofenadine hydrochloride				

Note: The duration of administration etc. could be modified according to the additional information obtained after preliminary safety report.

Laboratory Examination

	28 days before administration	Day 1 of administration	Day 29 of administration	Day 57 of administration	Day 72 of administration	15 days after completion
Plt($\times 10^4$/mm^3)	8.5	8.9	7.6	7.6	6.8	13.7
Alb(g/dL)	3.9	—	—	—	—	—
T-Bil(mg/dL)	1.5	1.6	2.9	4.0	—	—
D-Bil(mg/dL)	—	—	—	—	—	—
AST(IU/L)	41	66	36	34	31	—
ALT(IU/L)	38	91	37	31	27	—
ALP(IU/L)	153	—	—	—	—	—
γ-GTP(IU/L)	44	85	70	63	72	—
BUN(mg/dL)	16	15	11	—	—	—
Creatinine(mg/dL)	1.02	1.06	0.91	0.96	0.88	—
WBC(/mm^3)	8,500	12,100	4,500	5,200	4,900	6,300

	22 days after completion	25 days after completion	32 days after completion	43 days after completion	53 days after completion
Plt($\times 10^4$/mm^3)	15.8	6.7	7.0	6.0	5.9
Alb(g/dL)	—	2.8	2.6	2.8	1.8
T-Bil(mg/dL)	37.8	—	16.7	22.0	25.2
D-Bil(mg/dL)	—	—	12.7	18.7	20.0
AST(IU/L)	47	—	23	37	607
ALT(IU/L)	27	—	13	21	210
ALP(IU/L)	—	—	188	282	554
γ-GTP(IU/L)	83	—	59	84	76
BUN(mg/dL)	89	12	12	24	94
Creatinine(mg/dL)	6.75	1.7	2.0	2.06	9.15
WBC(/mm^3)	7,600	12,600	9,500	6,900	16,100

—:No data

Case3

Patient		Daily dose/ Treatment duration	Adverse reactions
Gender/ Age	Reason for Use (complications)		Clinical course and Treatment
Female 50s	Chronic hepatitis C (Diabetes mellitus)	100 mg /62 days	BW: approx. 90 kg, Height: approx. 160 cm History of varices oesophageal. (approx. 16.5 months ago) No history of allergy. No history of alcohol consumption. No history of adverse events with previous treatments. Hepatic chirrhosis before initiation of simeprevir sodium: None Pre-treatment: Child-pugh Score: Grade A (6 points), hepatic encephalopathy and ascites: None T-Bil: <2.0 mg/dL, Alb: 2.8-3.5（g/dL）、PT activity: ＞70% 17 days before administration: Plt: 6.6 x10^4/mm^3, T-Bil: 2.1 mg/dL Day1 of administration: Three drugs of combination therapy with simeprevir sodium (100 mg/day), peginterferon alfa-2a (180 μg/week), and ribavirin (800 mg/day) was started. Day 18 of administration: T-Bil: 4.8mg/dL Day 54 of administration: Jaundice developed. Day 59 of administration: Abdominal CT revealed that a finding of hepatic cirrhosis while no ascites was noted. Day 62 of administration (day of discontinuation): Hepatic failure developed. Treatment with simeprevir sodium was discontinued, and the patient was admitted to hospital. 8 days after discontinuation: The jaundice did not improve despite the discontinuation of the treatment with simeprevir sodium, then treatment with peginterferon alfa-2a and ribavirin was also discontinued. 13 days after discontinuation: Abdominal CT showed that pleural effusion and ascites. The patient experienced bacterial peritonitis. 19 days after discontinuation: The jaundice did not improve. Steroid pulse therapy was started (and continued for 5 days). 22 days after discontinuation: The jaundice and ascites retention became marked, and signs of spontaneous bacterial peritonitis were also noted, for which antibiotic treatment was intensified. 23 days after discontinuation: The jaundice worsened, and continuous haemodiafiltration was performed (and continued for 2 days).

Patient		Daily dose/ Treatment duration	Adverse reactions	
Gender/ Age	Reason for Use (complications)		Clinical course and Treatment	
			25 days after discontinuation	The patient experienced hepatic encephalopathy. Plasma exchange was performed (and continued for 2 days).
			27 days after discontinuation	In the early morning, the patient died. Outcome for hepatic failure and bacterial peritonitis: Death DLST test：Not performed Liver biopsy: Not performed
Concomitant drugs: rivabirin, peginterferon alfa-2a and mitiglinide calcium hydrate				

Laboratory Examination

	17days before administration	Day 1 of administration	Day 18 of administration	Day 59 of administration	9 days after discontinuation of SMV	26 days after discontinuation of SMV
Plt ($\times10^4$/mm^3)	6.6	5.9	5.4	9.7	11.8	3.8
Alb (g/dL)	3.5	3.6	3.1	2.5	2.4	3.1
T-Bil (mg/dL)	2.1	2.08	4.8	11.21	15.61	21.68
D-Bil (mg/dL)	0.32	—	1.69	7.14	10.73	17.36
AST (IU/L)	30	29	23	45	56	748
ALT (IU/L)	23	22	18	23	27	181
ALP (IU/L)	339	—	259	400	387	261
γ-GTP (IU/L)	47	44	40	40	36	38
RBC ($\times10^4$/mm^3)	404	399	284	321	319	290
Hb (g/dL)	14.2	14.1	9.8	11.1	10.9	10.1
Htc(%)	40.4	39.9	28.4	34.0	32.6	32.5
WBC (/mm^3)	4,600	4,800	1,500	3,400	4,600	17,700
CRP (mg/dL)	0.17	0.14	—	1.42	3.3	0.74

—：No data