■Cases where haermorrhages and abnormalities on tests of hemostasis associated with concomitant use of igratimod with warfarin were observed.

Case No.	Sex	Age	Adverse reactions	Seriousness	Daily dose	Latency time to onset of adverse reactions	Treatment by the drug	Outcome
1	Female	70's	Increased PT-INR Pulmonary alveolar haermorrhage	serious	50mg	12 days 41days	discontinuation	Recovery Death
2	Female	60's	Faecal occult blood positive Gingival bleeding Subcutaneous bleeding Anaemia	serious	25mg	23 days 12 days 14 days 23 days	discontinuation	Unknown Recovery Recovery Recovery
3	Male	80's	Puncture site haemorrhage Conjunctival haemorrhage	serious	25mg	29 days 29 days	discontinuation	Recovery Recovery
4	Female	70's	Increased PT-INR	Non-serious	25mg	28days	discontinuation	Unknown
5	Female	70's	Increased PT-INR	Non-serious	25mg	28days	continuation	Recovery
6	Female	60's	Increased PT-INR	Non-serious	25mg	unknown	unknown	Unknown
7	Female	50's	Increased PT-INR	Non-serious	25mg	14days	continuation	Recovery
8	Female	60's	Subcutaneous bleeding	Non-serious	50mg	109days	discontinuation	Recovery
9	Male	60's	Haematoma	Non-serious	25mg	15days	discontinuation	Recovery

■Case summaries

＜Case1＞

Patient		Daily dose/ Treatment duration	Clinical course and therapeutic measures	Outcome
Sex/ age	Reason for use（complications）			
Female ・ 70's	Rheumatoid arthritis (Atrial fibrillation) (Interstitial	25mg 31days 50mg 10days	Adverse reactions： Increased PT-INR Pulmonary alveolar haermorrhage	Recovery Death

	pneumonia) (Bronchitis chronic) (Insomnia) (Depression) (Osteoporosis) (Renal impairment)		16 years before administration	Rheumatoid arthritis (RA) developed.	
			6years before administration	Administration of warfarin potassium (3mg/day) was started.	
			6days before administration	The laboratory result showed PT-INR 1.34 due to administration of warfarin potassium (2.5mg/day).	
			Start date of administration	The dose of igratimod (25mg/day) was added because treatment with salazosulfapyridine, tacrolimus hydrate, and prednisolone could not control RA.	
			Day 2 of administration	PT-INR 1.35	
			Day 12 of administration	PT-INR increased to 2.94	
			Day 18 of administration	The dose of warfarin potassium was reduced to 2.0mg/day.	
			Day 22 of administration	PT-INR 2.29	
			Day 32 of administration	The dose of igratimod was increased to 50mg/day.	
			Day 41 of administration	Pulmonary alveolar haermorrhage occurred. The patient felt dyspnoea.	
			Day 42 of administration（Day of discontinuation）	Administration of igratimod was discontinued on the patient’s own judgment.	
			1 day after discontinuation	SpO_2 was in the range of 80%. PT-INR 7.18. The chest CT showed diffuse opacities. Pulmonary alveolar haermorrhage was suspected. The patient was diagnosed with pulmonary alveolar haermorrhage because Broncho-Alveolar Lavage Fluid (BALF) was bloody. The patient was admitted to a hospital. Pulse therapy with methylprednisolone (500mg) was carried out. Administrations of tazobactam sodium/piperacillin sodium and sulfamethoxazole/trimethoprim (4 tablets) were started.	
			2 days after	PT-INR 11.91. 4U of fresh frozen plasma (FFP) and menatetrenone (10mg) were	

			discontinuation	injected. Oral administration of menatetrenone (45mg/day) was started.	
			3 days after discontinuation	PT-INR 1.24. Because her breathing difficulty worsened, administration of morphine was started. Because Pneumocystis PCR was negative and β-D glucan level was negative; the dose of sulfamethoxazole/trimethoprim was reduced to preventive dosage. SpO_2 was 95% with a reservoir mask of 15 L/min oxygen.	
			After 3 days after discontinuation	Oxygenation did not improve. Respiratory depression by morphine occurred.	
			13 days after discontinuation	The patient died.	

Concomitant medications：warfarin potassium, salazosulfapyridine, prednisolone, tacrolimus hydrate, teprenone, sulindac, zolpidem tartrate, risedronate sodium

Clinical Laboratory Values：

Laboratory test items	6 days before administration	Day 2 of administration	Day 12 of administration	Day 22 of administration	Day 32 of administration	1 day after discontinuation
PT-INR	1.34	1.35	2.94	2.29	2.27	7.18
RBC (10^4/μL)	382		363		385	381
Hb (g/dL)	11.0		10.5		10.8	10.6

Laboratory test items	2 days after discontinuation	3 days after discontinuation	5 days after discontinuation	6 days after discontinuation	9 days after discontinuation
PT-INR	11.91	1.24	3.06	1.32	1.17
RBC (10^4/μL)	325	319	306		304
Hb (g/dL)	9.1	8.7	8.3		8.2

＜Case2＞

Patient		Daily dose/ Treatment duration	Clinical course and therapeutic measures	Outcome
Sex/ age	Reason for use (complications)			
Female ・	Rheumatoid arthritis	25mg 11days	Adverse reactions： Faecal occult blood positive	Unknown

60’s	(Hypertension) (Osteoporosis) (Atrial fibrillation) (Angina) (Venous thrombosis limb) (Hepatic steatosis) (Interstitial pneumonia)		Gingival bleeding Subcutaneous bleeding Anaemia		Recovery Recovery Recovery
				Administration of warfarin (3mg/day) was started.	
			Start date of administration	Administration of igratimod was started.	
			Day 11 of administration	Tingling tongue developed, pharynx pain occurred.	
			（Day of discontinuation）		
			1 day after discontinuation	Gingival bleeding was observed.	
			3 days after discontinuation	Subcutaneous bleeding in both thighs (+) was observed.	
			10 days after discontinuation	Because of subcutaneous bleeding in right forearm, front of both thighs, right lower leg, left buttock (++), dose of warfarin was reduced from 3mg/day to 2mg/day. Administration of etanercept was discontinued.	
			11 days after discontinuation	The patient was hard to awake in the morning due to general malaise. The patient presented facial pallor. Gingival bleeding had stopped. Administration of methotrexate was discontinued.	
			12 days after discontinuation	The patient was admitted to a hospital. Hb: 8.2g/dL, RBC :2,420,000/μL Faecal occult bleeding test was positive. Administration of warfarin was discontinued. Transfusion of packed red blood cell (400mL) was performed.	
			13 days after discontinuation	Transfusion of packed red blood cell 400mL was given.	
			16 days after discontinuation	Transfusion of packed red blood cell 400mL was given. In the afternoon, systemic subcutaneous bleeding remained unchange. The patient’s malaise disappeared. Her appetite was improved.	
			17 days after discontinuation	Peripheral blood test results showed normal value.	
			20 days after discontinuation	Systemic subcutaneous bleeding disappeared.	

			34 days after discontinuation	The patient was expected that she were able to be discharged from the hospital because of a full recovery. Later, she was discharged.	

Concomitant medications：: warfarin potassium, prednisolone, methotrexate, etanercept (genetic recombination), triamcinolone acetonide, ecabet sodium hydrate, fursultiamine hydrochloride, famotidine, furosemide, eldecalcitol, elcatonin,adsorbed influenza virus vaccine,nitroglycerin, celecoxib, minodronic acid hydrate

Clinical Laboratory Values：

Laboratory test items	36 days before administration	2 days after discontinuation	12 days after discontinuation	13 days after discontinuation	14 days after discontinuation	17 days after discontinuation	32 days after discontinuation
PT-INR	3.89		3.23		1.16		
RBC (10^4/μL)	362	396	242	284		411	426
Hb (g/dL)	12.7	13.4	8.2	9.4		13.7	14.6

＜Case3＞

Patient		Daily dose/ Treatment duration	Clinical course and therapeutic measures		Outcome
Sex/ age	Reason for use (complications)				
Male・ 80’s	Reumatoid arthritis (Atrial fibrillation) (Renal impairment) (Peripheral arterial occlusive disease) (Osteoporosis)	25mg 28days	Adverse reactions： Bleeding from a site of puncture Conjunctival haemorrhage		Recovery Recovery
				A clinic <A> prescribed warfarin to the patient. He maintained stable PT-INR levels (1.5-2.0).	
			Start date of administration	A orthopedic hospital <B> started administration of igratimod (25mg) The patient took a routine medical chekup at A. PT-INR 1.5	
			Day 29 of administration （ Day of discontinuation）	Because uncontrolled bleeding from a site of injection received at B, the patient visited the A. Hemostasis of the site of puncture was difficult, and PT-INR increased to 8.0. Conjunctival haemorrhage of the left eye was observed. The patient was admitted to A. Administration of warfarin was discontinued. Administration of igratimod was discontinued. Oral administration of menatetrenone (15mg) was started and the bleeding stooped.	
			1 day after discontinuation	The patient was discharged from A because the events recovered. PT-INR 1.8	
			7 days after	Administration of warfarin (2mg/day) was resumed.	

			discontinuation 28 days after discontinuation	The patient had continued to receive warfarin (2mg/day) with good PT-INR control (1.7).	
Concomitant medications : warfarin potassium, prednisolone, sarpogrelate hydrochloride, acetaminophen, rebamipide, diclofenac sodium, etanercept, alprostadil, furosemide, spironolactone, allopurinol, famotidine, folic acid, mizoribine					

Details of revision（extract passages）

<table>
<tr><th>After the revision</th><th>Before the revision</th></tr>
<tr><td>【Contraindications】
1. Pregnant women or women who may become pregnant

[Results of the laboratory animal study（rat）showed teratogenicity, increased rate of early fetal death and oetal ductus arteriosus systole (Please refer to the section of “administration to pregnant women, parturient women and nursing women, etc”.).]

2. Patients with severe liver disorder
(Because hepatic dysfunction may occur, as an adverse drug reaction, there is a risk that liver disorder can be further aggravated)

3. Patients with peptic ulcer
(Because peptic ulcer may occur, as an adverse drug reaction, there is a risk that peptic ulcer can be further aggravated)

4. Patients with a prior hypersensitivity to the ingredients of the drug

5. Patients who are taking warfarin
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<tr><td>3. Interaction
(1)Contraindication to the concomitant use（Patients should not use the following drug concomitantly with igratimod）
<table><tr><th>Name of drugs</th><th>Clinical conditions・treatments</th><th>Action mechanism・risk factors</th></tr><tr><td>Warfarin（warfarine etc.）</td><td>Severe cases of haemorrages</td><td>unknown</td></tr></table></td><td>3. Interaction
Caution with the concomitant use
<table><tr><th>Name of drugs</th><th>Clinical conditions・treatments</th><th>Action mechanism・risk factors</th></tr><tr><td>Non-Steroidal Anti-Inflammatory Drugs (NSAID)</td><td colspan="2">The statement is omitted</td></tr></table></td></tr>
</table>

	associated with the concomitant use of the drug and warfarin due to intensify the effect of warfarin have been reported. When patients are required to receive warfarin therapy, they should not be administered the drug and put a high priority of warfarin therapy.	

(2)Caution with the concomitant use

Name of drugs	Clinical conditions・treatments	Action mechanism・risk factors
Non-Steroidal Anti-Inflammatory Drugs (NSAID)	The statement is omitted（no change）	
Cimetidine	The statement is omitted（no change）	
Phenobarbital	The statement is omitted（no change）	

~~Warfarin~~	~~Because the effect of warfarin may be intensified,this drug should be carefully administered such as adjusting the dose~~	~~unknown~~
Cimetidine	The statement is omitted	
Phenobarbital	The statement is omitted	

（____）: edit（Revision by the notification from Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health. Labor and Welfare,dated May17, 2013）