Pharmaceuticals and Medical Devices Safety Information

No. 384 July 2021

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No. 384 July 2021

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Labour and Welfare, Japan

[Outline of Information]

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E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of Precautions, *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
CPMS	Clozaril Patient Monitoring Service
CT	Computed tomography
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency

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Blood Monitoring and Rechallenge with Clozapine

1. Introduction

Clozapine preparations (branded name: Clozaril Tablets, hereinafter referred to as “clozapine”) are used as a drug for treatment-resistant schizophrenia. Safety measures have been implemented for clozapine since its marketing approval in Japan in April 2009 focused on patient monitoring by the Clozaril Patient Monitoring Service (hereinafter referred to as "CPMS"), which is a procedure prescribed for early detection of serious adverse reactions that may occur with clozapine such as agranulocytosis.

Based on the deliberation in the 7th FY2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as “the Subcommittee on Drug Safety”) held on May 24, 2021, issues such as the frequency of blood monitoring or criteria for considering rechallenge have been revised recently. This section will introduce the details of the revision.

2. Background

Clozapine was first approved overseas in Austria in October 1969, but in Finland, where it was approved in January 1975, 16 cases of agranulocytosis were reported including 8 deaths in the first 6 months after launch and measures to suspend clozapine in the market or to discontinue development were taken in affected countries. Subsequently, the effectiveness of clozapine in patients with schizophrenia refractory to existing antipsychotics was recognized and then, based on a claim that introduction of patient monitoring designed for the prevention, early detection, and treatment of agranulocytosis that may occur with clozapine was shown to reduce the mortality rate due to agranulocytosis, clinical development was conducted limited in patients with schizophrenia who are unresponsive or intolerant to other drugs and clozapine was approved and marketed as a result.

Given such backgrounds, patient monitoring has been conducted in Japan by the CPMS since the time of its marketing approval as mentioned above. Blood tests once a week for the first 26 weeks, and once every other week after Week 26 of administration were specified in the package insert and the CPMS operating procedure of clozapine.

"Patients who have once discontinued clozapine according to the discontinuation criteria on blood tests specified in the CPMS" and "patients with a history of agranulocytosis or severe neutropenia" have been listed in the CONTRAINDICATIONS section of the package insert as well.

On the other hand, the CPMS operating procedure stipulates that rechallenge of clozapine may be permitted if the following 4 conditions are met, subject to the review at the Clozaril Proper Use Committee [note)], and such rechallenge has actually been carried out.

Condition 1: At least 18 weeks must have elapsed from the start of treatment with clozapine before discontinuation due to a white blood cell count < 3 000/mm^3 or a neutrophil count < 1 500/mm^3.

Condition 2: Patients must not have developed agranulocytosis (neutrophil count < 500/mm^3)

Condition 3: The CPMS-registered physician has denied the relationship between clozapine and onset of decreased white blood cell/neutrophil count.

Condition 4: The patient or his/her legal representative wants rechallenge with clozapine and has given his/her consent.

Note: This is a third-party committee established by Novartis Pharma K.K., the MAH of clozapie, which consists of experts (physicians, pharmacists, and bioethics or legal experts) and is responsible for monitoring and providing guidance on proper CPMS operation, and approving

revisions to the CPMS operating procedures.

While these safety measures were in place, the Japanese Society of Psychiatry and Neurology (JSPN), the Japanese Society of Clinical Neuropsychopharmacology (JSCNP), the Japanese Society of Neuropsychopharmacology (JSNP), and Japanese Society of Schizophrenia Research (JSSR) jointly submitted a request seeking that (1) blood test intervals after Week 52 of administration be revised to once every 4 weeks, (2) the CPMS criteria for considering rechallenge be relaxed, and (3) administration of clozapine be permitted to patients with a history of granulocytopenia or severe neutropenia.

The request described that the incidence of granulocytopenia is approximately 1% in Japan as well as overseas, rarely occurring after Week 52 of administration, and the blood test interval is once every 4 weeks overseas. The request also noted an opinion that complete denial by the CPMS-registered physician of the relationship between clozapine and the observed decrease in white blood cell or neutrophil counts, as the requirement by the current CPMS for rechallenge, is difficult even if the drug and events are reasonably considered unrelated.

Taking into account the request from the academic societies mentioned above, MHLW decided to consider revision of the package insert and the CPMS operating procedure.

3. Deliberation by the Subcommittee on Drug Safety

Description in overseas package inserts, published literature, related guidelines, standard textbooks in Japan and overseas, incidences of granulocytopenia, etc. in Japan, and status of rechallenge were investigated and the results are as follows:

(1) Blood test intervals after Week 52 of administration
- It cannot be concluded that incidences of decreased neutrophil count and granulocytopenia are higher in Japan than overseas.
- In several overseas countries/regions where the blood test frequency after Week 52 was initially once every 2 weeks, no apparent problems have been reported since the frequency was revised to once every 4 weeks.
- No new safety concerns have been identified following the extension of the blood test interval to 42 days under the state of emergency declaration in Japan.

(2) Rechallenge after discontinuation due to a decreased white blood cell count or decreased neutrophil count
- Rechallenge is actually carried out in Japan and overseas and no evident problems have been reported in patients to whom clozapine was rechallenged.

(3) Use of clozapine in patients with a history of agranulocytosis or severe neutropenia
- There have been no reports that a history of agranulocytosis or severe neutropenia which are considered due to factors other than clozapine is a risk of clozapine-induced agranulocytosis.
- In several overseas countries/regions, patients with a history of agranulocytosis or severe neutropenia, which is considered to be due to factors other than clozapine, is not listed as a contraindication, and no clinically evident problems have been reported.

Following the above deliberation, the Subcommittee on the Drug Safety concluded that the package insert of clozapine may be revised as follows:

- A statement should be added to the IMPORTANT PRECAUTIONS section that blood tests may be reduced to once every 4 weeks after Week 52 of administration.
- The current language "Patients who have once discontinued clozapine according to the discontinuation criteria on blood tests specified in the CPMS" in the CONTRAINDICATION section should be revised to "patients who have discontinued clozapine according to the discontinuation criteria on blood tests specified in the CPMS and do not meet the criteria for considering rechallenge specified in the CPMS.” A statement should be added to the IMPORTANT PRECAUTIONS section that the CPMS-specified haematologist, etc. should be consulted for the decision on whether to rechallenge clozapine, and if rechallenge is permitted,

blood tests should be performed at the same frequency as with the initial administration.

- "Patients with a history of agranulocytosis or severe neutropenia" should be removed from the CONTRAINDICATIONS section and a cautionary statement that clozapine should be administered in collaboration with the CPMS-specified haematologists, etc. should be added to the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section.

The committee also concluded that requirements of the criteria for considering rechallenge in the CPMS operating procedure may be revised to permit rechallenge if the CPMS-registered physician considers clozapine unrelated to the observed decreased white blood cell/neutrophil count, the patients or their legal representatives want to resume clozapine, and have given their consent, subject to a review at the Clozaril Proper Use Committee.

4. Closing remarks

Healthcare professionals are requested to understand the gist of this revision and carefully check the revised package insert for a careful decision on the revision of blood test frequency and administration of clozapine to patients such as those who have once discontinued the drug according to the discontinuation criteria on blood tests specified by the CPMS. Continued cooperation by healthcare professionals for proper use of clozapine would be appreciated.

[References]

・Materials 1-1 to 1-5 of the 7th FY 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on May 24, 2021)
https://www.mhlw.go.jp/stf/newpage_18697.html (only in Japanese)

・Revision of Precautions (PSEHB/PSD Notification No. 0603-1 dated June 3, 2021)
https://www.mhlw.go.jp/content/11120000/000787755.pdf (only in Japanese)
English translation by PMDA (June 3, 2021 Clozapine)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0009.html

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Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated June 15, 2021, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Pembrolizumab (genetical recombination)

Branded name (name of company)	Keytruda Injection 100 mg (MSD K.K.)
Therapeutic category	Other antitumor agents
Indications	Malignant melanoma Unresectable advanced or recurrent non-small cell lung cancer Relapsed or refractory classical Hodgkin lymphoma Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy Advanced or recurrent, microsatellite instability-high (MSI-H) solid tumours that have progressed after cancer chemotherapy (limited to patients who are refractory or intolerant to standard treatments) Radically unresectable or metastatic renal cell carcinoma Recurrent or metastatic head and neck cancer Radically unresectable advanced or recurrent PD-L1-positive esophageal squamous cell cancer that has progressed after cancer chemotherapy

PRECAUTIONS (revised language is underlined)

[Under new instructions]

8. IMPORRANT PRECAUTIONS	<u>Fulminant hepatitis, hepatic failure,</u> hepatic impairments, or sclerosing cholangitis may occur. Patients should be carefully monitored through periodical hepatic function tests (more frequently for co-administration with axitinib).
11. ADVERSE REACTIONS	<u>Fulminant hepatitis, hepatic failure,</u> hepatic impairment, hepatitis, sclerosing cholangitis
11.1 Clinically Significant Adverse Reactions	<u>Fulminant hepatitis, hepatic failure,</u> hepatic impairment accompanied by elevated levels of AST, ALT, γ-GTP, Al-P, bilirubin, etc., hepatitis, or sclerosing cholangitis may occur.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period (April 2018 to March 2020) Cases involving hepatic failure : 5 (3 patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 33 600 Japanese market launch: February 2017

Case Summary 1

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 80s	Lung squamous cell carcinoma stage IV (atrial fibrillation) (hypertension) (emphysema)	200 mg 1 course every 3 weeks (2 courses in total)	**Drug-induced fulminant hepatitis**	
				56 days before administration	HBsAg: -, HBcAb: +, 2.63, HBsAb: +, 33.3, HCVAb: -
				1 day before administration	T-Bil: 1.0 mg/dL, D-Bil: 0.2 mg/dL, AST: 24 U/L, ALT: 11 U/L, LD: 251 U/L, ALP: 222 U/L, γ-GTP: 17 U/L, antinuclear antibody: 40>
				Day 1 of administration	The 1st course of keytruda alone as the 1st-line therapy was administered for the treatment of non-small cell lung cancer (first-episode, histological type: Squamous cell carcinoma, primary site: Left lower lobe, Stage IV, T3N0M1c, PD-L1 TPS:10%, metastasis to other sites) Complication: Emphysema, hypertension, atrial fibrillation Medical history: Cholelithiasis Radiation therapy: 36 Gy (vertebra) Smoking history: 50 cigarettes per day, 46 years Medication history: Denosumab (only once) Performance Status: 0, Karnofsky Performance Status: 90 The patient had no liver and biliary tract disease (alcoholic hepatitis, hepatic cirrhosis, nonalcoholic fatty liver disease, cholangitis, etc.), viral hepatitis, metastases to liver, shock/hypotension, drugs with hepatotoxicity (pre-administration and concomitant drugs), history of adverse reactions, drinking history, and allergies.
				5 days after administration	HBsAg: -, HBV DNA: -, HCV RNA: -
				8 days after administration	Total protein: 6.8 g/dL, albumin: 3.6 g/dL, T-Bil: 1.0 mg/dL, AST: 22 U/L, ALT: 12 U/L, LD: 235 U/L, ALP: 245 U/L, γ-GTP: 18 U/L, platelet: 13.5x10000/mm^3, eosinophil count: 120/mm^3, eosinophil fraction: 3.3%, CRP: 0.31 mg/dL
				27 days after administration (Final administration)	The 2nd course of keytruda was administered (final administration). Before administration of keytruda: Total protein : 6.8 g/dL, albumin: 3.6 g/dL, T-Bil: 1.8 mg/dL, AST: 482 U/L, ALT: 410 U/L, LD: 235 U/L, ALP: 356 U/L, γ-GTP: 53 U/L, platelet: 13.7x10000/mm^3, CRP: 0.55 mg/dL
				4 days after termination	Although his family sensed something was slightly wrong with him, the patient was able to go on walks. Fatigue and behavioral abnormalities were noted.
				9 days after termination	Apparent abnormal speech and behavior started.
				10 days after termination (day of onset)	The patient had visual hallucination and disturbed consciousness associated with hepatic impairment. Total protein: 6.7 g/dL, albumin: 3.5 g/dL, T-Bil: 12.8 mg/dL, D-Bil: 7.1 mg/dL, AST: 2900 U/L, ALT: 1993 U/L, LD: 1279 U/L, ALP: 426 U/L, γ-GTP: 131 U/L, platelet: 17.4x10000/mm^3, CRP: 0.41 mg/dL, ammonia: 155 μg/dL.
				11 days after termination	The patient visited the ER with a complaint of apparent abnormal behavior and itching. Disturbed consciousness and systemic

				yellowing were observed. Biochemical test revealed severe liver disorder. T-bil: 13.7 mg/dL, D-Bil: 7.5 mg/dL, AST: 2600 U/L, ALT: 1985 U/L, LD: 1102 U/L, ALP: 435 U/L, γ-GTP: 138 U/L, HBsAg: -, HBcAb: +, 3.61, HBsAb: +, 25.9, HCVAb: -, HBV DNA: -, HCV RNA: - Suspected of having fulminant hepatitis, the patient consulted with a gastroenterologist. Abdominal CT revealed no obvious changes in the liver and no abnormalities in the liver morphology. The patient was diagnosed with drug-induced fulminant hepatitis. Administration of methylprednisolone sodium succinate 80 mg once/day was initiated immediately for the treatment of fulminant hepatitis (2 days).
			12 days after termination	The steroids did not improve drug-induced fulminant hepatitis. General condition and blood test showed no improvement. Total protein: 6.7g/dL, albumin: 3.4 g/dL, T-Bil: 15.5 mg/dL, D-Bil: 7.8 mg/dL, AST: 1643 U/L, ALT: 1684 U/L, LD: 983 U/L, ALP: 436 U/L, γ-GTP: 144 U/L, platelet: 19.6x10000/mm^3, CRP: 0.47 mg/dL, ammonia: 215μg/dL, PT%: 10%, PT (Sec): 67.2 sec, PT-INR: 5.31 INR
			13 days after termination	The patient died of drug-induced fulminant hepatitis. Autopsy, liver biopsy, liver supporting therapies other than steroids (glycyrrhizin preparations, ursodeoxycholic acid, etc.), other treatments (liver transplant, plasma exchange, haemofiltration dialysis, etc.) were not performed. The onset of hepatic encephalopathy was unknown.

Laboratory test value

Tests (unit)	56 days before admin.	44 days before admin.	1 day before admin.	5 days after admin.	8 days after admin.	27 days after admin. (final admin)	10 days after termi-nation (day of onset)	11 days after termi-nation	12 days After termi-nation
Total protein (g/dl)	-	6.7	-	-	6.8	6.8	6.7	-	6.7
Albumin (g/dl)	-	3.5	-	-	3.6	3.6	3.5	-	3.4
T-Bil (mg/dL)	-	1.0	1.0	-	1.0	1.8	12.8	13.7	15.5
D-Bil (mg/dL)	-	-	0.2	-	-	-	7.1	7.5	7.8
AST (U/L)	-	21	24	-	22	482	2 900	2 600	1 643
ALT (U/L)	-	12	11	-	12	410	1 993	1 985	1 684
LD (U/L)	-	254	251	-	235	235	1 279	1102	983
ALP (U/L)	-	359	222	-	245	356	426	435	436
γ-GTP (U/L)	-	40	17	-	18	53	131	138	144
Platelet (10 000/mm^3)	-	14.4	-	-	13.5	13.7	17.4	-	19.6
Eosinophil count (/mm^3)	-	-	-	-	120	-	-	-	-
Eosinophil fraction (%)	-	-	-	-	3.3	-	-	-	-
CRP (mg/dL)	-	0.46	-	-	0.31	0.55	0.41	-	0.47
HBsAg	Negative	-	-	Negative	-	-	-	Negative	-
HBcAb	Positive 2.63	-	-	-	-	-	-	Positive 3.61	-
HBsAb	Positive 33.3	-	-	-	-	-	-	Positive 25.9	-
HCVAb	Negative	-	-	-	-	-	-	Negative	-
HBV DNA	-	-	-	Negative	-	-	-	Negative	-
HCV RNA	-	-	-	Negative	-	-	-	Negative	-
Antinuclear antibody	-	-	40>	-	-	-	-	-	-

Ammonia (μg/dL)	-	-	-	-	-	-	155	-	215
PT% (%)	-	63	-	-	-	-	-	-	10
PT(Sec) (sec)	-	15.3	-	-	-	-	-	-	67.2
PT-INR (INR)	-	1.28	-	-	-	-	-	-	5.31

Concomitant drugs: None

Case Summary 2

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
2	Male 50s	Renal cell carcinoma stage IV (Unknown)	200 mg 1 course every 3 weeks (2 courses in total)	**Fulminant hepatitis, hepatic failure, tumour lysis syndrome, hepatorenal syndrome** 16 days before administration: T-Bil: 0.3 mg/dL, AST: 11 U/L, ALT: 14 U/L, ALP: 276 U/L, Cre: 1.07 mg/dL, BUN: 24.9 mg/dL, K: 4.5 mEq/L, UA: 6.9 mg/dL Day 1 of administration: The 1st course of keytruda in combination with axitinib as 1st line therapy was administered for the treatment of renal cell carcinoma (first episode, histological type: Clear cell carcinoma, primary site: Right kidney, Stage: IV, TNM classification: cT3aN2M1, IMDC risk classification: Intermediate, PD-L1 TPS: No test, metastasis to other sites). Medical history: Hypertension Radiation therapy: 40 Gy (thoracic spine) Smoking history: 15 cigarettes per day/32 years Drinking history: Yes Performance Status: 3, Karnofsky Performance Status: 50. The patient had no liver and biliary tract disease (alcoholic hepatitis, hepatic cirrhosis, nonalcoholic fatty liver disease, cholangitis, etc.), viral hepatitis, metastases to liver, shock/hypotension, drugs with hepatotoxicity (pre-administration and concomitant drugs), history of adverse reactions, and allergies. 21 days after administration (Final administration): The 2nd course of keytruda was administered (final administration). The 1st course was without problems. The patient continued outpatient treatment from the 2nd course. T-Bil: 0.3 mg/dL, AST: 31U/L, ALT: 58 U/L, ALP: 396 U/L, Cre: 0.61 mg/dL, BUN: 16.1 mg/dL, K: 4.8 mEq/L, UA: 4.4 mg/dL Although the patient experienced anorexia, malaise and physical deconditioning, he was unable to go to hospital due to time constraints. The patient was at home for taking a wait-and-see approach. 19 days after termination (Day of onset): The patient made an emergency visit due to fatigue, vomiting, nausea, malaise, anorexia, jaundice, oliguria, elevated liver enzymes and disturbed consciousness. Blood test revealed abnormal hepatic function and electrolyte abnormality. Hepatic encephalopathy developed. Coma level classification (Inuyama classification): Ⅱ Abdominal CT: Ascites and stomach contents retention were noted. The tumor had a shrinking lesion. T-Bil: 6.5 mg/dL, AST: 4 805 U/L, ALT: 6 084 U/L, ALP: 1 382 U/L, NH3: 191μg/dL, Cre: 1.49 mg/dL, BUN: 56.8 mg/dL, IP: 6.6 mg/dL, K: 7.3 mEq/L, UA: 11.7 mg/dL Glucose/insulin (GI) was performed due to high K levels. Tumour lysis syndrome was suspected, and massive fluid infusion was performed. Treatment was started with allopurinol. Oral administration of axitinib was continued until 19 days after completion of keytruda. 20 days after administration: Renal function deteriorated. Urine output decreased. Hepatic enzyme decreased. Blood purification and steroid treatment were considered. Consultations with a

				21 days after termination	gastroenterologist and hepatologist were conducted. The patient was considered to have drug-induced hepatic impairment and electrolyte abnormality due to tumour lysis. Anticancer drugs were discontinued for taking a wait-and-see approach T-Bil: 6.8 mg/dL, AST: 3 598 U/L, ALT: 4 998 U/L, ALP: 1 175 U/L, Cre: 2.4 mg/dL, BUN: 61.4 mg/dL, K: 6.2 mEq/L, UA: 13.5 mg/dL. Decreased oxygenation and decreased level of consciousness were noted. Blood test revealed aggravated renal function and decreased hepatic enzyme. It was determined that the blood tests results were part of the clinical course of hepatic failure after fulminant hepatitis. The patient was diagnosed with hepatorenal syndrome associated with hepatic failure. T-Bil: 7.3 mg/dL, AST: 1 986 U/L, ALT: 3 335 U/L, ALP: 982 U/L, NH3: 402μg/dL, PT-INR: 6.35 INR, PT%: 5%, HBsAg (qualitative): (-), HBc antibody/CLIA (determination): (-), HCVAb (qualitative): (-), HA-IgM antibody (determination): (-), CMV-IgM (determination): (-), EBV anti VCAIgM/FA: <10 times, anti-mitochondrial antibody M2 /FEIA (determination): (-), antinuclear antibody: <40, IgG: 1619 mg/dL, Cre: 4.17 mg/dL, BUN: 65.2 mg/dL, IP: 4.7 mg/dL, K: 6.6 mEq/L, UA: 12.9 mg/dL. Informed consent was obtained from the patient's family. They did not wish life-prolonging treatment. The patient was poorly controlled, and his condition deteriorated. The patient died of fulminant hepatitis, hepatic failure, renal failure (hepatorenal syndrome), and tumour lysis syndrome. Autopsy and liver biopsy were not performed.

Laboratory test value

Tests (unit)	16 days before admin.	21 days before admin.	19 days after termination (day of onset)	20 days after termination	21 days after termination
T-Bil (mg/dL)	0.3	0.3	6.5	6.8	7.3
AST (U/L)	11	31	4 805	3 598	1 986
ALT (U/L)	11	58	6 084	4 998	3 335
ALP (U/L)	276	396	1 382	1 175	982
Ammonia (μg/dL)	—	—	191	—	402
PT-INR (INR)	—	—	—	—	6.35
PT% (%)	—	—	—	—	5
HBsAg	—	—	—	—	Negative
HBc antibody/CLIA (determination)	—	—	—	—	Negative
HCVAb (qualitative)	—	—	—	—	Negative
HA-IgM antibody (determination)	—	—	—	—	Negative
CMV-IgM (determination)	—	—	—	—	Negative
EBV anti VCAIgM/FA	—	—	—	—	<10 times
Anti-mitochondrial antibody M2/FEIA (determination)	—	—	—	—	Negative
Antinuclear antibody	—	—	—	—	<40
IgG (Mg/dL)	—	—	—	—	1 619
Cre (mg/dL)	1.07	0.61	1.49	2.4	4.17
BUN (mg/dL)	24.9	16.1	56.8	61.4	65.2
IP (mg/dL)	4.5	4.8	7.3	6.2	6.6
K (mEq/L)	3.3	—	6.6	—	—
UA (mg/dL)	6.9	4.4	11.7	13.5	12.9

Concomitant drugs: Acetaminophen, duloxetine hydrochloride, magnesium oxide, azilsartan, amlodipine besilate, silodosin, oxycodone hydrochloride hydrate

2 Ixekizumab (genetical recombination)

Branded name (name of company)	Taltz Subcutaneous Injection Autoinjectors 80 mg, Taltz Subcutaneous Injection Syringes 80 mg (Eli Lilly Japan K.K.)
Therapeutic category	Agents affecting metabolism, n.e.c. (not elsewhere classified)
Indications	Treatment of the following diseases in patients who have had an inadequate response to conventional therapies: Psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis Ankylosing spondylitis, non-radiographic axial spondyloarthritis

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Interstitial pneumonia Cases of interstitial pneumonia have been reported. If cough, dyspnea, or pyrexia, etc. are observed, examinations such as chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period (April 2018 to March 2021) Cases involving interstitial pneumonia : 4 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 4 200 Japanese market launch: November 2016

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 50s	Psoriasis vulgaris		**Medical history: Suspected eosinophilic oesophagitis** **No medical history of pneumonitis** **Complication: Asthma** **Allergic history: Yes (pyrazolone drugs)** **Drinking and smoking history: Unknown** **History of biological preparations use: None (diagnosed with psoriasis 25 years ago)**	
				13 days before administration	Chest computed tomography (CT) findings: No interstitial shadows were noted. (pleural thickening and nodule shadow only)
				Day 1 of administration	Administration of ixekizumab 160 mg for the treatment of psoriasis vulgaris was initiated.
				14 days after administration	Ixekizumab 80 mg was administered. (Thereafter, administered every 2 weeks)
				98 days after administration (Day of final administration)	Ixekizumab 80 mg was administered.
				103 days after administration (Day of onset)	The patient had symptoms of “wheezing” breathing on exertion and shortness of breath when going up the stairs. T-SPOT test: Negative Chest X-ray test revealed no abnormal findings in the thorax. The central shadow showed no mass or deviation. In the lung field, linear shadows and diffuse pale patchy shadows were noted in the bilateral middle lower lungs.
				104 days after administration	The patient was diagnosed with suspected interstitial pneumonia by a radiologist.
				113 days after administration	Dry cough developed.
				119 days after administration	The patient visited the respiratory medicine. The patient had subjective symptoms of dyspnoea on exertion. Percutaneous oxygen saturation (SpO_2): 95% (room air) Chest CT revealed many patchy ground glass areas with elevated density dominant in the bilateral upper lobes in the lung field. In the periphery, linear to reticular lesions were observed. No tumors or enlarged lymph nodes in the mediastinum or hilar region were noted. No pleural effusions were noted either. Sputum test, bronchoalveolar lavage, and drug lymphocyte stimulation test, etc. of ixekizumab were not performed. Drug-induced pneumonia and viral pneumonia were suspected, but the patient was diagnosed with drug-induced lung disorder. Ixekizumab was discontinued. Administration of prednisolone 30 mg was initiated on an outpatient basis.
				126 days after administration	Subjective symptoms were alleviated. SpO_2: 98% (room air) Chest X-ray test revealed shadows in the peripheral areas of bilateral lungs remained but tended to disappear. Prednisolone was reduced to 20 mg.
				140 days after administration	Subjective symptoms were improved. Chest X-ray test revealed shadows in the peripheral lung fields mostly disappeared. Prednisolone was reduced to 15 mg.

			161 days after administration	The patient recovered from drug-induced lung disorder.
			266 days after administration	Chest CT revealed areas of elevated concentration in the lung field of bilateral lungs were reduced. No tumors or enlarged lymph nodes in the mediastinum or hilar region were noted. No pleural effusions were noted either. On the whole, the patient was not considered to have eosinophilic pneumonia.

Laboratory test value

Tests (unit)	standard value	13 days before admin.	103 days after admin. (day of onset)	119 days after admin.	126 days after admin.	140 days after admin.	160 days after admin.	266 days after admin.
Hemoglobin (g/dL)	13.3-16.6	15.3	14.9	15.9	15.9	15.6	15.4	
White blood cell ($x10^3$/μL)	3.8-9.1	11.7	7.6	7.7	9.5	9.5	8.4	
Platelet count ($x10^4$/μL)	15.5-35.4	28.5	29.1	32.4	37.9	31.5	36.4	
Segmented cell (%)	41-73.5		53.8					
Lymphocytes (%)	19.2-48.1		35.9					
Eosinophils (%)	0.4-7.9		3.0					
Eosinophil count (/μL)	150-300	164	228	270	10	19	17	
AST (U/L)	13-33	16	24	23	14	16	14	
ALT (U/L)	6-30	25	27	25	20	23	21	
LDH (U/L)	119-229		227					
CRE (mg/dL)	0.6-1.1	0.85	0.78	0.87	0.86	0.83	0.8	
KL-6 (U/mL)	0-500		661					123
β-D glucan (pg/mL)	0-6		6.0					

Concomitant drugs: Calcipotriol hydrate/betamethasone dipropionate, olopatadine hydrochloride, betamethasone butyrate propionate, vilanterol trifenatate/fluticasone furoate

3
Revision of Precautions (No.324)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated June 1, 3, 15, 2021.

1 Agents affecting metabolism, n.e.c. (not elsewhere classified)
Diclofenac etalhyaluronate sodium

Branded name	Joyclu 30 mg intra-articular injection (Seikagaku Corporation)
[Under New instructions]	
(newly added)	1. WARNINGS Serious shock and anaphylaxis may occur following administration of this drug. Sufficient preparation for emergency responses should be ensured prior to administration. Patients should be carefully monitored after administration of this drug.
8. IMPORTANT PRECAUTIONS (newly added)	Serious shock and anaphylaxis may occur following administration of this drug. Sufficient preparation for emergency responses should be ensured prior to administration. Patients should be carefully monitored during and after administration of this drug. Patients and their caregivers, etc., should be adequately informed that shock and anaphylaxis may occur, with signs and symptoms, and that patients should seek medical attention immediately if any abnormalities are observed.
11. ADVERSE REACTIONS	
11.1. Clinically Significant Adverse Reactions	Shock, anaphylaxis
11.1.1	

2 Psychotropic agents
Clozapine

Branded name	Clozaril Tablets 25 mg, 100 mg (Novartis Pharma K.K.)
[Under New instructions]	
2. CONTRAINDICATIONS	Patients who have discontinued this drug according to the discontinuation criteria for blood tests specified in the CPMS and do not meet the criteria for considering rechallenge specified in the CPMS (Agranulocytosis may occur.)
	(Deleted)
8. IMPORTANT PRECAUTIONS	If a white blood cell count below 3 000/mm^3 or a neutrophil count below 1 500/mm^3 (the range (3) below) is noted, administration of this drug should immediately be discontinued and the CPMS-specified haematologist, etc. be contacted. Blood tests should be performed every day until these counts have recovered to the range (1), at least once every week for 4 weeks or longer after the recovery. Patients should be carefully monitored for signs of infection (such as cold-like symptoms including pyrexia and pharyngeal pain) and counter-infection or other appropriate measures should be taken. Patients in whom this drug has been discontinued as a result of a

decrease in the white blood cell or neutrophil counts to the range (3) in the table below must not be rechallenged with this drug unless they meet the criteria for considering rechallenge even if these counts have recovered after the discontinuation. The CPMS-specified haematologist, etc. should be consulted for the decision on rechallenge. If rechallenge is deemed necessary, blood tests should be performed once every week for the first 26 weeks of rechallenge. Blood tests may be reduced to once every other week after Week 26, and to once every 4 weeks after Week 52 of rechallenge if conditions are met. Recurrence of leukopenia or neutropenia in a short period of time following rechallenge with this drug has been reported.

If white blood cell counts and neutrophil counts for the first 26 weeks of administration meet either of the conditions below and administration is temporarily discontinued for a reason other than blood disorder and for a duration shorter than a week, blood tests after such a temporary discontinuation may be performed at the frequency prior to the temporary discontinuation. If administration is resumed after a temporary discontinuation for a week or longer, blood tests should be performed once every week for the first 26 weeks of resumed administration. Blood tests may be reduced to once every other week after Week 26, then to once every 4 weeks after Week 52 of resumed administration if conditions are met.

- Both counts remain in the range (1) in the table below.
- White blood cell counts decreased to < 4 000/mm^3 and ≥ 3 500/mm^3 with neutrophil counts ≥ 2 000/mm^3 then recovered to the range (1).

Table) Initiation/discontinuation criteria and testing frequency during administration with clozapine

	WBC (/mm^3)	NC (/mm^3)	Treatment
(1)	4 000 or higher and 2 000 or higher		Administration may be initiated. Administration may be continued. Blood tests should be performed once every week for the first 26 weeks of administration. Blood tests may be reduced to once every other week after Week 26, then to once every 4 weeks after Week 52 of administration if conditions are met. If administration is temporarily discontinued for up to 4 weeks after switching to once every other week or once every 4 weeks, blood tests should be performed once every week for the first 26 weeks of resumed administration. Blood tests may be reduced to once every other week after Week 26 and to once every 4 weeks after Week 52 of resumed administration if conditions are met.
(2)	3 000 or higher and below 4 000 or 1 500 or higher and below 2 000		Administration may be continued with blood tests performed twice every week or more often until recovery to the range (1) and patients carefully monitored.

(3)	Below 3 000 or below 1 500	Administration should be discontinued immediately. Blood tests should be performed every day until recovery to the range (1) and adequate counter-infection measures should be taken. Blood tests should be performed at least once every week for 4 weeks or longer after recovery.

Cases of eosinophilia have been reported. If an eosinophil count of 3 000/mm^3 or higher is noted, administration should preferably be discontinued. If any abnormalities are observed, appropriate measures should be taken such as consulting the CPMS-specified haematologist, etc. Administration should be resumed only when the eosinophil count has recovered to below 1 000/mm^3.

Cases of thrombocytopenia have been reported. If a platelet count below 50 000/mm^3 is noted, administration should preferably be discontinued. If any abnormalities are observed, appropriate measures should be taken such as consulting the CPMS-specified haematologist, etc.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
9.1 Patients with Complication or History of Diseases, etc.
(newly added)

Patients who have once discontinued this drug according to the discontinuation criteria for blood tests specified in the CPMS (excluding those who do not meet the criteria for considering rechallenge specified in the CPMS)
Agranulocytosis may occur. This drug should be administered under the coordination with the CPMS-specified haematologist, etc. In patients who discontinued this drug according to the discontinuation criteria for blood tests specified in the CPMS, recurrence of events related to cytopenia such as agranulocytosis has been reported as occurring in a shorter period of time with greater severity when they were rechallenged than in the initial administration.

Patients with a history of agranulocytosis or severe neutropenia
This drug should be administered under the coordination with the CPMS-specified haematologist, etc. Agranulocytosis may occur.

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3 Agents affecting metabolism, n.e.c. (not elsewhere classified)

Ixekizumab (genetical recombination)

Branded name
Taltz Subcutaneous Injection Autoinjectors 80 mg,
Taltz Subcutaneous Injection Syringes 80 mg (Eli Lilly Japan K.K.)

[Under New instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions
(newly added)

Interstitial pneumonia
Cases of interstitial pneumonia have been reported. If cough, dyspnea, or pyrexia, etc. are observed, examinations such as chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

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4 Other antitumor agents

Pembrolizumab (genetical recombination)

Branded name
Keytruda Injection 100 mg (MSD K.K.)

[Under New instructions]

8. IMPORRANT PRECAUTIONS	Fulminant hepatitis, hepatic failure, hepatic impairments, or sclerosing cholangitis may occur. Patients should be carefully monitored through periodical hepatic function tests (more frequently for co-administration with axitinib).
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Fulminant hepatitis, hepatic failure, hepatic impairment, hepatitis, sclerosing cholangitis Fulminant hepatitis, hepatic failure, hepatic impairment accompanied by elevated levels of AST, ALT, γ-GTP, Al-P, bilirubin, etc., hepatitis, or sclerosing cholangitis may occur.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect adverse drug reactions (ADRs) data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 31 May 2021)
◎: Products for which EPPV was initiated after May 1, 2021

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Upadacitinib hydrate Rinvoq Tablets 7.5 mg, 15 mg[*1]	AbbVie GK	May 27, 2021
◎	Palonosetron hydrochloride Aloxi I.V. injection 0.75 mg, Aloxi I.V. infusion bag 0.75 mg	Taiho Phamaceutical Co., Ltd.	May 27, 2021
◎	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) COVID-19 Vaccine Moderna Intramuscular Injection[*2]	Takeda Pharmaceutical Company Limited.	May 24, 2021
◎	Ofatumumab (genetical recombination) Kesimpta for s.c. injection 20 mg pen[*3]	Novartis Pharma K.K.	May 24, 2021
◎	Polatuzumab vedotin (genetical recombination) Polivy for Intravenous Infusion 140 mg, 30 mg[*4]	Chugai Pharmaceutical Co., Ltd.	May 19, 2021
◎	Pabinafusp alfa (genetical recombination) Izcargo for I.V. infusion 10 mg[*5]	JCR Pharmaceuticals Co., Ltd.	May 19, 2021
◎	Denileukin diftitox (genetical recombination) Remitoro for Intravenous Drip Infusion 300 μg[*6]	Eisai Co., Ltd.	May 19, 2021
◎	Diclofenac etalhyaluronate sodium Joyclu 30 mg intra-articular injection[*7]	Seikagaku Corporation	May 19, 2021
◎	Anhydrous sodium sulfate/potassium sulfate/magnesium sulfate hydrate Sulprep Combination Solution[*8]	Nihon Pharmaceutical Co., Ltd.	May 19, 2021
	Galcanezumab (genetical recombination) Emgality Subcutaneous Injection 120 mg Autoinjectors, Emgality Subcutaneous Injection 120 mg Syringe*[9]	Eli Lilly Japan K.K.	April 26, 2021
	Idursulfase beta (genetical recombination) Hunterase ICV Injection 15 mg*[10]	Clinigen K.K.	April 26, 2021

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Baricitinib Olumiant tablets 2 mg, 4 mg*[11]	Eli Lilly Japan K.K.	April 23, 2021
Brigatinib Alunbrig Tablets 30 mg, 90 mg*[12]	Takeda Pharmaceutical Company Limited.	April 23, 2021
Berotralstat hydrochloride Orladeyo Capsules 150 mg*[13]	OrphanPacific, Inc.	April 23, 2021
Molidustat sodium Musredo tablets 5 mg, 12.5 mg, 25 mg, 75 mg*[14]	Bayer Yakuhin Ltd.	April 22, 2021
Dimethyl sulfoxide Zymso Intravesical Solution 50%*[15]	Kyorin Pharmaceutical Co., Ltd.	April 21, 2021
Anamorelin hydrochloride Adlumiz Tablets 50 mg*[16]	Ono Pharmaceutical Co., Ltd.	April 21, 2021
Acalabrutinib Calquence capsules 100 mg*[17]	AstraZeneca K.K.	April 21, 2021
Delgocitinib [1] Corectim Ointment 0.25% [2] Corectim Ointment 0.5%	Japan Tobacco Inc.	March 23, 2021
Ferric citrate hydrate*[18] Riona Tab. 250 mg	Japan Tobacco Inc.	March 23, 2021
Lascufloxacin hydrochloride Lasvic Intravenous Drip Infusion Kit 150 mg	Kyorin Pharmaceutical Co., Ltd.	March 1, 2021
Thalidomide*[19] Thaled Capsules 25, 50, 100	Fujimoto Pharmaceutical Corporation	February 24, 2021
Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Comirnaty intramuscular injection	Pfizer Japan Inc.	February 16, 2021
Semaglutide (genetical recombination) Rybelsus tablets 3 mg, 7 mg, 14 mg	Novo Nordisk Pharma Ltd.	February 5, 2021
Rivaroxaban*[20] Xarelto tablets 15 mg, 10 mg, Xarelto fine granules 15 mg, 10 mg, Xarelto OD tablets 15 mg, 10 mg	Bayer Yakuhin Ltd.	January 22, 2021
Cetuximab sarotalocan sodium (genetical recombination) Akalux IV Infusion 250 mg	Rakuten Medical Japan K.K.	January 1, 2021
Recombinant adsorbed quadrivalent human papillomavirus virus-like particle vaccine (yeast origin) *[21] Gardasil Aqueous Suspension for Intramuscular Injection Syringes	MSD K.K.	December 25, 2020
Baricitinib*[22] Olumiant tablets 4 mg, 2 mg	Eli Lilly Japan K.K.	December 25, 2020
Midazolam Buccolam Oromucosal Solution 2.5 mg, 5 mg, 7.5 mg, 10 mg	Takeda Pharmaceutical Company Limited.	December 10, 2020
Enarodustat	Japan Tobacco Inc.	December 8,

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
	Enaroy tablets 2 mg, 4 mg		2020
	Incobotulinumtoxin A Xeomin 50 units for Intramuscular injection, Xeomin 100 units for Intramuscular injection, Xeomin 200 units for Intramuscular injection	Teijin Pharma Limited.	December 4, 2020

*1 Psoriatic arthritis in patients who have responded inadequately to conventional therapy

*2 Prevention of infectious disease caused by SARS-CoV-2

*3 Prevention of relapse and delaying the accumulation of physical disability in patients with relapsing-remitting multiple sclerosis and patients with active secondary progressive multiple sclerosis

*4 Relapsed or refractory diffuse large B-cell lymphoma

*5 Mucopolysaccharidosis II

*6 Relapsed or refractory peripheral T-cell lymphoma and relapsed or refractory cutaneous T-cell lymphoma

*7 Osteoarthritis (in the knee and hip joints)

*8 Elimination of intestinal contents as pretreatment prior to colonoscopy

*9 Preventive treatment of migraine

*10 Mucopolysaccharidosis II

*11 SARS-CoV2 pneumonia (limited to patients requiring supplemental oxygen)

*12 Unresectable, advanced or recurrent ALK fusion gene-positive non-small cell lung cancer

*13 Suppression of the onset of attacks in acute hereditary angioedema

*14 Nephrogenic anaemia

*15 Improvement of symptoms of interstitial cystitis (Hunner type) (chronic pelvic pain, pressure and discomfort associated with the bladder, lower urinary tract symptoms such as increased urgency or pollakiuria)

*16 Cancer cachexia in malignant tumors of non-small cell lung cancer, gastric cancer, pancreatic cancer, or colorectal cancer

*17 Relapsed or refractory chronic lymphocytic leukaemia (including small lymphocytic lymphoma).

*18 Iron deficiency anaemia

*19 Crow-Fukase (POEMS) syndrome

*20 Treatment and reduction in the risk of recurrence of venous thromboembolism

*21 Prevention of the following diseases caused by infection with human Papillomavirus (HPV) Types 6, 11, 16, and 18
・Cervical cancer (squamous cell carcinoma and adenocarcinoma) and its precancerous lesions (cervical intraepithelial neoplasia (CIN) grades 1, 2 and 3 and cervical adenocarcinoma *in situ* (AIS))
・Vulval intraepithelial neoplasia (VIN) grades 1, 2 and 3 and vaginal intraepithelial neoplasia (VaIN) grades 1, 2 and 3
・Anal cancer (squamous cell carcinoma) and its precancerous lesions (anal intraepithelial neoplasia (AIN) grades 1, 2, and 3)
・Condyloma acuminatum
(Only underlined diseases in men are subject to EPPV)

*22 Atopic dermatitis with inadequate response to conventional treatments