Pharmaceuticals and Medical Devices Safety Information

No. 345 August 2017

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 345 August 2017

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

[Outline of Information]

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
AIH	Autoimmune hepatitis
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AMED	Japan Agency for Medical Research and Development
ANA	Antinuclear antibody
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
AUS	Abdominal ultrasonography
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CBD	Common bile duct
CHD	Cholecytohepatic duct (or Common hepatic duct)
CRP	C-reactive protein
CT	Computed tomography
D-Bil	Direct bilirubin
DI	Drug Information
DLST	Drug lymphocyte stimulation test
EBV-IgM	Epstein-Barr virus immunoglobulin M
EPPV	Early Post-marketing Phase Vigilance
ERCP	Endoscopic retrograde cholangiopancreatography
EST	Endoscopic sphincterotomy
EUS	Endoscopic ultrasonography
FY	Fiscal year
HA	Hepatitis A
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBV-DNA	Hepatitis B virus-Deoxyribonucleic acid
HCV	Hepatitis C virus
HHV-6	Human herpesvirus 6
HPB	Health Policy Bureau
IDUS	Intraductal ultrasound
IgE	Immunoglobulin E
IgG	Immunoglobulin G
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MMF	Mycophenolate mofetil
mPSL	Methylprednisolone sodium succinate
MRCP	Magnetic resonance cholangiopancreatography
NSCLC	Non-small cell lung cancer
PAB	Pharmaceutical Affairs Bureau
P-ANCA	Perinuclear anti-neutrophil cytoplasmic antibody
PD	Progressive disease
PMDA	Pharmaceuticals and Medical Devices Agency
PS	Performance status
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PSL	Prednisolone
S3	Segment 3 (left lateral inferior segment of hepatic lobe)
S4	Segment 4 (left medial segment of hepatic lobe)

S7	Segment 7 (right posterior superior segment of hepatic lobe)
S8	Segment 8 (right anterior superior segment of hepatic lobe)
SD	Stable disease
SOL	Space-occupying lesion
T-Bil	Total bilirubin
TNM	Tumour-node-metastasis
WBC	White blood cells
γ-GTP	gamma-glutamyl transpeptidase

1

Summary of Guidance for Adverse Drug Reaction Reporting by Medical and Pharmaceutical Providers

1. Introduction

Reporting of adverse drug reactions (ADRs) is managed under two systems: Company reporting and medical institution reporting. Company reporting is the system where manufacturing authorization holders (MAH) report ADRs to PMDA after collecting the information from medical institutions/pharmacies, which is stipulated in the Law for Ensuring the Quality, Efficacy and Safety of Drugs and Medical Devices at the Pharmaceutical and Medical Device Act Article 68-10(1). Medical institution reporting is the system where pharmaceutical providers such as physicians or pharmacists directly report to PMDA, stipulated in the Pharmaceutical and Medical Device Act Article 68-10(2). Reports from companies have increased every year with approximately 51,000 cases whereas reports from medical institutions have practically leveled off with approximately 6,100 cases in fiscal 2015. (Figure 1)

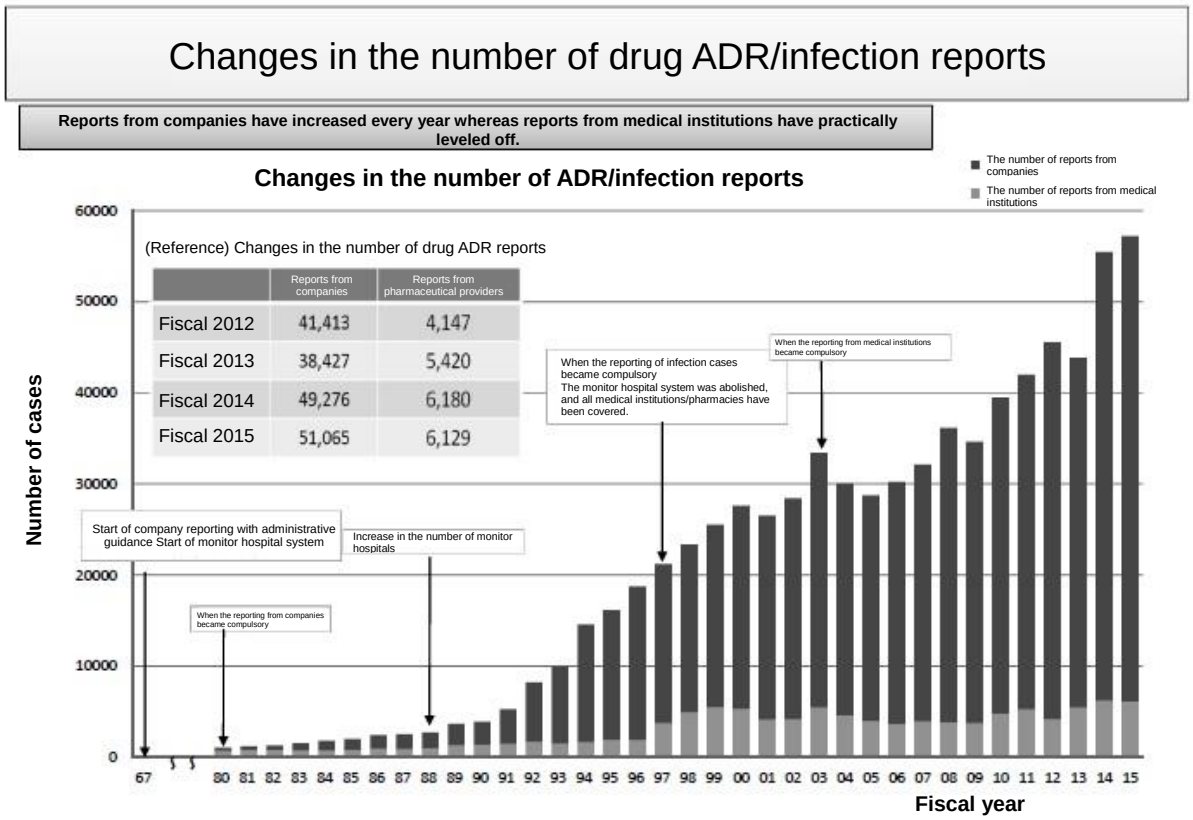

Figure 1

On the other hand, in recent years, changes in the environment surrounding the safety of drugs have been observed, such as, diverse use of drugs produced by various MHA as driven by the promotion of using generics, and multiple adverse effects not previously seen with single drug regimens, reflecting the aging society and multiple drug treatment such as multi-drug regimens for cancer treatment. .

In “the Study of Promotion of Adverse Drug Reaction Reporting by Leveraging the Functions of Pharmacy/Department of Pharmacy” of the FY 2016 Health and Labour Administration Promotion Research Project (the Health and Labour Sciences Special Research Project) (The study representative Professor Koichi Masuyama in School of Pharmacy, Tokyo University of Pharmacy and Life Science) integrated applicable cases in terms of promotion of ADR reporting by medical and pharmaceutical providers and prepared “the Summary of Guidance for Adverse Drug Reaction Reporting by Medical and Pharmaceutical Providers” (draft) with a focus on interprofessional within an institution and interinstitutional collaboration involving out-of-hospital pharmacies (Figure 2). You can see the details of the Summary of Guidance below, which was issued dated July 10, 2017 with a partial change in the contents based on the discussion in the 2nd meeting of the Subcommittee for Pharmaceuticals and Medical Devices Regulation of the Health Science Council of MHLW on June 22, 2017.

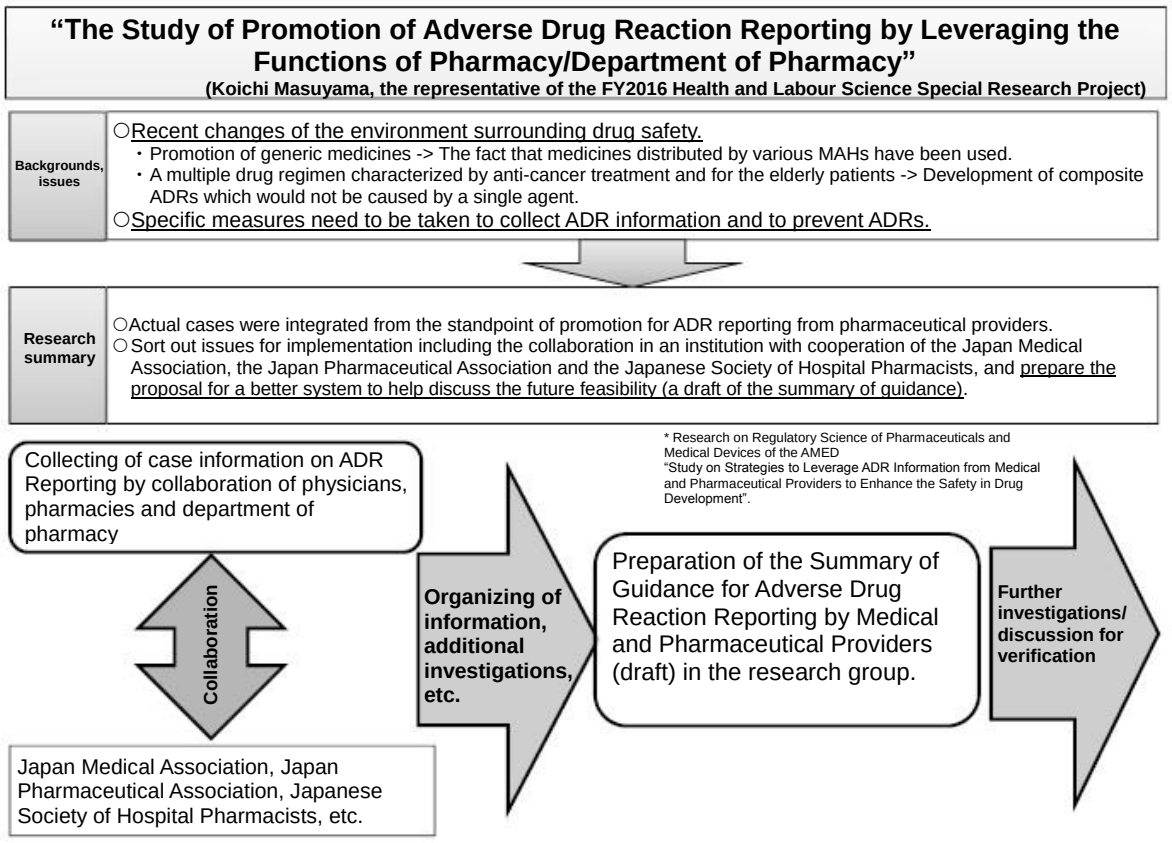

Figure 2

2. Summary of Guidance for Adverse Drug Reaction Reporting by Medical and Pharmaceutical Providers

(Administrative Notice Attachment by Safety Division, General Affairs Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated July 10, 2017)

This summary of the guidance's purpose is to promote ADR reporting from medical institutions in "the Study of Promotion of Adverse Drug Reaction Reporting by Leveraging the Functions of Pharmacy/Department of Pharmacy" (Koichi Masuyama, the representative of the FY 2016 Health and Labour Science Special Research Project). Therefore, the summary provides the expected points to keep in mind when medical institutions - and pharmacies together in some cases - report ADRs with a suspected relation to prescription drugs so that the summary can help medical institutions and other medical and pharmaceutical providers smoothly proceed with ADR reporting operations.

The Guidance will be enhanced by further investigating and examining the status and feasibility of ADR reporting in various medical institutions.

[Keys of Guidance]

○ In recent years, the environment surrounding pharmaceutical safety has been changing. Generic prescription drugs (generic drugs) have been widespread and polypharmacy has caused composite ADRs, which would not happen with a single drug, in many patients including the elderly.

○ Medical and Pharmaceutical providers are required to make efforts to prevent ADRs which may affect patients as much as they can. In addition, they need to collaborate between every profession in an institution and between institutions including out-of-hospital pharmacies in order to find any first sign and alleviate the extent of ADRs which have occurred in patients and to submit required ADR reporting.

ADR reporting by medical institutions to the authority (PMDA and MHLW) is specified in Article 68-10(2) (hereinafter, “Drugs and Medical Devices Safety Reporting System”) of the Pharmaceutical and Medical Device Act. Medical institutions are required to take necessary actions based on the significance.

(Pharmaceutical and Medical Device Act Article 68-10(2)) Proprietors of pharmacies; proprietors of hospitals or clinics for human beings or human-reared animals; or physicians, dentists, pharmacists, registered sales clerk, veterinarians and other medical professionals shall, in the case where they learn of the occurrence of any disease, disability or death suspected to be caused by the side effects from use of the pharmaceuticals, medical devices or regenerative medicine products, or the occurrence of any infectious disease suspected to be caused by the use of such items, and when it is found to be necessary in order to prevent the occurrence or spread of hazards to public health and hygiene, report the same to the Minister of Health, Labour and Welfare. (The reports are required to be submitted to PMDA as specified in Pharmaceutical and Medical Device Act Article 68-13(3)).

○ ADR reporting requires providing information which identifies multiple prescribed drugs and generics. Based on this, we outlined what medical institutions should do to promote direct reporting to the authority (PMDA) by leveraging the Drugs and Medical Devices Safety Reporting System.

[ADRs which require expedited reporting]

○ MAHs report to the authority (PMDA) serious ADRs obtained from medical and pharmaceutical providers with the outcome of death, hospitalization or more serious within 15 days or 30 days according to the seriousness assessment methods in the attachment of “Criteria for Seriousness Classification of ADRs, etc.” (PAB/SD Notification No. 80 issued by the Director of Safety Division, Pharmaceutical Affairs Bureau (PAB), Ministry of Health and Welfare dated June 29, 1992) When medical and pharmaceutical providers report ADRs directly to the authority (PMDA) in the report forms specified by the Drugs and Medical Devices Safety Reporting System, the following issues (*) should be considered. In addition, medical institutions should read the attachment of the relevant notice as well, as a reference regarding the seriousness of cases (described later).

(*) Refer to the following criteria regardless of the description in the package inserts even if the causal relationship is not evident.

[1] Fatal
[2] Disabilities
[3] Cases that may lead to fatalities
[4] Cases that may lead to disabilities
[5] Cases requiring hospitalization or prolonging duration of hospitalization for treatment at the hospital or clinic (excluding cases noted in [3] and [4])
[6] Serious cases in accordance with cases noted in [1] to [5]
[7] Congenital disorders or abnormalities in later generations
[8] Occurrence of infectious disease cases suspected to occur due to the use of relevant drugs, medical devices, regenerative medicine products, etc.
[9] Of the malfunctions that occur due to the use of relevant medical devices, regenerative medicine products, etc., those with the risk of occurrence of cases, etc. noted in [1] to [7].
[10] Besides the cases noted in [1] to [8], occurrence of cases which are not mild and could not be predicted based on the package insert, etc.
[11] Of the malfunctions that occur due to the use of relevant medical devices, regenerative medicines, etc., those with the risk of occurrence of cases noted in [10].

Source: "Revisions in practices of reporting ADRs, infections, and malfunctions from medical institutions, etc. regarding drugs, medical devices, or regenerative medical products" (PSEHB Notification No. 0325-4 by the Director of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated March 25, 2016)

[Handling of ADR information in medical institutions]

○ Medical institutions should submit an ADR reporting when patients experience an ADR with a suspected relation to drugs which needs treatment, causes abnormal laboratory findings, or considerably affects their daily living. The authority (PMDA) horizontally evaluates the ADR reporting accumulation status in more than one medical institution and possible measures for proper use of drugs. Medical and Pharmaceutical providers, too, are expected to contribute to the efforts.

○ As for acute diseases, for example, some of the drugs may cause a certain number of ADRs in a relatively short period of time though the drugs will be effective according to the patient's condition. In contrast, some chronic diseases might not yield an ADR until after a year or two of continuous administration. Therefore medical institutions are expected to ascertain and report ADRs according to patient's conditions when required. Medical institutions should also provide necessary information to local clinics and pharmacies so that the patient can be followed up when moving into home care.

○ To submit ADR reports without delay (to the MAH and to the authority [PMDA and MHLW]) and to help enhance healthcare and hygiene when cases with suspected ADRs reportable to the authority (PMDA) emerge, medical institutions should specify in advance and share the communication method, writing format, items to report between diagnosis and treatment departments as well as between such departments and department of pharmacy within an institution.

- To collaborate with an appropriate department especially when a disease suspected to be a serious ADR is not routinely treated by the prescribing department, medical institutions should specify the in-house procedures and communication methods.

○ When information on cases with suspected ADRs is shared between doctors of different departments, the department of pharmacy, and other support divisions in an institution, in order to ensure that all the cases for whom the same ADRs are suspected are managed after the initial occurrence, the medical institution should assign the manager to collect and manage all information for regulatory reporting and the prior information of cases until the onset of the ADR in the institution (narratives, laboratory results, other descriptions in the medical record, compliance status, etc.). The responsibilities are expected to rest with medical safety management offices, pharmaceutical safety management supervisors, DI-office, department of pharmacy, etc.

- When a disease which results in hospitalization is suspected to be an ADR, it is desirable to collaborate with the manager in charge of all the information and to obtain details including the patient's clinical course prior to hospitalization and medications when considering subsequent reporting of the ADR expected. At the same time, all prescribed drug information should be obtained from the referral hospital, the primary

pharmacy, the patient or their family.

- ○ In addition, under the supervision of the manager above, all information on cases with suspected ADRs within the institution should be collected, effectively reviewed and understood.
- ○ Manuals are available for management of individual serious ADRs prepared by the academic society of each field and issued by the MHLW, specifically to secure the opportunities for differential diagnosis and early detection of an ADR for other departments. (http://www.info.pmda.go.jp/juutoku/juutoku_index.html) (only available in Japanese language)
- ○ The relevant department of medical institutions need to closely communicate with the department of pharmacy to identify prescribed/administered drugs, compliance and assess the relationship between drugs and diseases suspected to be an ADR. It is especially important that physicians play a major role in deciding on the diagnosis and treatment. The other roles like regulatory reporting should be shared by other people, such as pharmacists in the department of pharmacy or DI office, or the pharmaceutical safety management supervisor. The institution should determine the role assignment in advance to avoid delay in necessary ADR reporting.
  - For example, it is desirable to extract the relevant cases from the following hospital databases and employ them when reporting to the authority (PMDA).
    - ✧ Incident report database
    - ✧ Cases of pharmaceutical intervention (database)
    - ✧ DI office inquiries database
- ○ Events for which a causal relationship with drugs are unclear or known ADRs should be reported to the MAHs or reporting to the authority (PMDA) in the report forms specified by the Drugs and Medical Devices Safety Reporting System should be considered. When multiple concomitant medications of a patient make it difficult to identify the single suspect drug, or to report various MAHs of concomitant medications, etc., reporting to the authority (PMDA) in the report forms specified by the Drugs and Medical Devices Safety Reporting System may have priority.
- ○ As a reference to consider the necessity of ADR reporting, the Attachment of “Criteria for Seriousness Classification of ADRs, etc.” (PAB/SD Notification No. 80 issued by the Director of Safety Division, PAB, Ministry of Health and Welfare).
  - ADRs of the liver, the kidneys, blood, hypersensitivity symptoms, the respiratory organs, the gastrointestinal organs, the circulatory organs, psycho-neurotic system, metabolic electrolyte abnormality are divided into the following 3 grades based on the seriousness:
    - ✧ Grade 1: Mild ADR
    - ✧ Grade 2: Neither serious nor mild ADR
    - ✧ Grade 3: ADR considered serious, which may be fatal or has the risk of causing permanent dysfunction that hinders daily living depending on the patient’s predisposition or condition when pyrexia is observed.

    Take into account that cases classified into Grade 1 or 2 should be reported when accompanied with suspected ADRs that are not noted in the precautions, or when they qualify as Grade 3.
- ○ Take into account that a Grade 3 ADR should be reported within 15 to 30 days in consideration of the public health and hygiene priority. This is not compulsory because the Drugs and Medical Devices Safety Reporting System does not set the deadline of reporting to the authority (PMDA) from the onset of the disease suspected to be an ADR.
- ○ Initial ADR reports do not have to provide the details. The details may be subsequently covered in the follow-up reports.
- ○ Follow the procedures below for a disease suspected to be an ADR in patients who received drugs by out-of-hospital prescription.

- Specifically, take into account the fact that poor compliance and adverse events are more common in the elderly receiving 6 or more drugs.
- Generics could have been dispensed to patients with an out-of-hospital prescription. Try to find the dispensing pharmacy to make an inquiry about the prescribed drug name for identification purposes, as required. The name is also available in the medication record book of the patient. When the pharmacy finds that the medical institution which made the inquiry did not issue the prescription, it should provide the information with the prescribing institution.
- The institution should ask the pharmacy to provide the available information on the patient's compliance for the drugs dispensed in a different pharmacy or prescribed in a different medical institution. (If the ADR report is submitted by the medical institution that made the inquiry, the information should be distributed to other institutions via the pharmacy. See [ADR handling at pharmacy].)
- When any condition suspected to be an ADR in a patient is reported in a tracing report from pharmacists, etc., the institution confirms the condition at the patient's visit or consultation to determine the required treatment and whether the ADR is reportable.

[ADR handling at pharmacy]

○ To contribute to the safe drug supply and proper use of drugs, pharmacies are expected to detect any first signs of a possible ADR when dispensing drugs to patients, to recommend that the patient see the prescribing physician, to provide information, or to discuss the reportability to the authority (PMDA) as required when the ADR is just suspected.

Pharmacies should provide the relevant explanation and try to have patients understand details on major ADRs of the drugs dispensed, the time of onset and the duration for the ADRs on the initial dispensing of high-risk drugs.

- Anti-cancer agents, coagulants, or other medications with high risks of fall in elderly patients.

○ Pay attention to signs for concerns about compliance and ADRs when checking and adjusting the unused drugs.

- Specifically, take into account the fact that poor compliance and adverse events are more common in the elderly receiving 6 or more drugs.

○ As the conditions which require attention, ask patients if they have experienced any of the following events/situations since the drug administration was started.

1) Dizziness, drowsiness, headache
2) Outcomes of injuries etc. caused by the above symptom(s).
3) Details of when an ADR was suspected and if the patient saw a physician for any reasons other than the primary disorder and received treatment.
4) Other conditions which may disrupt everyday life

- Dosage and administration of the drugs as well as surrounding details should be confirmed if information such as if a patient's laboratory results of creatinine clearance and the name of the disease together with the prescription were provided by the medical institution the patient visited.

○ When development of an ADR is suspected in a patient, give feedback on this to the prescribing medical institution in a tracing report or other methods. Comprehensively examine a patient's concomitant medications including those dispensed by different pharmacies, based on the medication record book of the patient.

○ Consider reporting any cases with a suspected ADR which requires treatment or is not considered to be mild (refer to the above [ADRs which require expedited reporting]), in cooperation with the prescribing medical institution to which a tracing report was sent, to the authority (PMDA) in the report forms specified by the Drugs and Medical Devices Safety Reporting System, when required, even if the relationship with the drug is not necessarily evident or the ADR is a known one. (See [Handling of ADR information in medical institutions].)

- When a medical institution reports ADRs to the authority (PMDA), pharmacists should provide the institution with the names of the drugs they dispensed and supplied (including those prescribed by other institutions - which should be given the details, too -) and information available on the patient's compliance.
- When a pharmacy reports an ADR to the authority (PMDA) in a situation where all information is shared on a physician's diagnosis of ADRs, a patient's outcomes, and laboratory results which are indicative of ADRs, the name of the prescribing medical institution should also be present along with the name of pharmacy when submitting the report.

Note: The wording has been slightly amended and the contents have also been partially changed based on the discussion in the 2nd meeting of the Subcommittee for Pharmaceuticals and Medical Devices Regulation of the Health Science Council of MHLW.

3. Conclusion

We are exploring more practical contents for this summary of the guidance through further empirical research and evaluation in order to promote ADR reporting by medical and pharmaceutical providers in “the Study on Strategies to Leverage ADR Information from Medical and Pharmaceutical Providers to Enhance the Safety in Drug Development”, Research on Regulatory Science of Pharmaceuticals and Medical Devices of the Japan Agency for Medical Research and Development (AMED).

We hope medical and pharmaceutical providers will leverage this summary of the guidance for smooth reporting from medical institutions or in collaboration with pharmacies and medical institutions for ADRs with a suspected relation to prescription drugs.

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated July 4, 2017, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Loxoprofen sodium hydrate (dermatologic preparation)

Brand name (name of company)	Loxonin Pap 100 mg, Loxonin Tape 50 mg, 100 mg (Lead Chemical Co., Ltd.), Loxonin Gel 1% (Daiichi Sankyo Co., Ltd.), Loxoprofen Na Spray 1% YD (Yoshindo Inc.), and others
Therapeutic category	Epidermides-Analgesics, anti-itchings, astringents, anti-inflammatory agents
Indications	Anti-inflammation/Pain relief in the following diseases and symptoms Osteoarthritis, myalgia, post-traumatic pain/swelling

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock or anaphylaxis (decreased blood pressure, urticaria, laryngeal oedema, dyspnoea, etc.) may occur. Patients should be carefully monitored. If any abnormalities are observed, use of this drug should be discontinued immediately and appropriate measures should be taken.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years (April 2014 to April 2017)
Cases related to shock, anaphylaxis: 2 cases (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 21,000,000

Launched in Japan: Loxonin Pap 100 mg: May 2006
Loxonin Tape 50 mg, 100 mg: July 2008
Loxonin Gel1%: October 2010
Loxoprofen Na Spray 1% YD: June 2015

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Treatment duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/
Age</th><th>Reason for use
(complications)</th><th>Clinical course and Therapeutic measures</th></tr>
<tr><td>1</td><td>Male
40s</td><td>Pain in extremity
pain
(none)</td><td>Unknown
for 1 day</td><td>Anaphylactic shock
Past history: Anaphylactic shock, asthma, urticaria
Day 1 of administration: The patient had pasta with spinach, mushroom, and salmon. The patient experienced pain on the left dorsum pedis and received loxoprofen sodium hydrate.
1 day after administration: In the morning, urticaria developed. The patient visited the emergency department in the reported medical institution. Facial pallor, cold sweat, systemic wheals developed. Somnolence was observed. Blood pressure: 79/39 mmHg. For treatment, adrenaline 0.3 mL was administered intramuscularly, plus dexamethasone sodium phosphate 6.6 mg and chlorpheniramine maleate 10 mL were administered intravenously. Somnolence persisted with blood pressure in the normal range. The patient was admitted to the hospital for follow up. After the patient's admission, no notable changes were observed in the patient's general condition.
2 days after administration: The patient was discharged from the hospital. Fexofenadine hydrochloride was administered.</td></tr>
<tr><td></td><td colspan="4">Laboratory Examination
Skin prick test
<table><tr><td></td><td>39 days after administration:</td></tr><tr><td>Loxoprofen sodium</td><td>Negative</td></tr><tr><td>Wheat</td><td>Negative</td></tr><tr><td>Spinach</td><td>Negative</td></tr><tr><td>Mushroom</td><td>Negative</td></tr><tr><td>Salmon</td><td>Negative</td></tr></table>IgE test
<table><tr><td></td><td>10 days after administration:</td></tr><tr><td>Total IgE (IU/mL)</td><td>271</td></tr></table></td></tr>
<tr><td></td><td colspan="4">Concomitant medications: none</td></tr>
</table>

2 a. Fluconazole
b. Fosfluconazole

Brand name (name of company)	a. Diflucan Capsules 50 mg, 100 mg, Diflucan Dry Syrup 350 mg, 1400 mg, Diflucan Intravenous Solution 50 mg, 100 mg, 200 mg (Pfizer Japan Inc.), and the others b. Prodif Intravenous Solution 100 mg, 200 mg, 400 mg (Pfizer Japan Inc.)
Therapeutic category	Chemotherapeutics-Miscellaneous
Indications	a. Capsules: The following infections with Candida or Cryptococcus Fungemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis Prophylaxis of deep mycosis in hematopoietic stem cell transplant patients Vaginitis and vulvovaginitis due to Candida Dry Syrup and Injections: The following infections with Candida or Cryptococcus Fungemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis Prophylaxis of deep mycosis in hematopoietic stem cell transplant patients b. The following infections with Candida or Cryptococcus Fungemia, respiratory mycosis, fungal peritonitis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	Drug-induced hypersensitivity syndrome: Initial symptoms of pyrexia and rash, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic function disorder, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken. Symptoms are often accompanied by virus reactivation such as human herpes virus type 6 (HHV-6). Caution should be exercised against recurrence or prolongation of rash, pyrexia, and hepatic function disorder, etc. that may occur even after discontinuation of administration.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years (April 2014 to April 2017) Cases related to drug-induced hypersensitivity syndrome: a. 1 case (no fatal case) b. 0 cases The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 190,000 Launched in Japan:

a. Diflucan Capsules 50 mg, 100 mg: June 1989, Diflucan Dry Syrup 350 mg, 1400 mg: June 2012, Diflucan Intravenous Solution, 100 mg, 200 mg: July 2006
b. January 2004

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Treatment duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/
Age</th><th>Reason for use
(complications)</th><th>Clinical course and Therapeutic measures</th></tr>
<tr><td>1</td><td>Female
50s</td><td>Cryptococcal pneumonia
(none)</td><td>Unknown
for a month</td><td>Drug reaction with eosinophilia and general symptom.

Day 1 of administration: Oral administration of fluconazole was started.

1 month after administration: (day of discontinuation) Liver disorder and erythema with severe pruritus on the limbs and trunk developed. Drug allergy was suspected, and fluconazole was discontinued. Liver disorder and skin eruption temporarily improved.

1 week after discontinuation: The body temperature was in the 39 degrees Celsius range with skin eruption and liver function aggravated, which led to the referral to the dermatology department.
At the patient's first consultation with a dermatologist, notable swelling face, difficulty in eye opening and generalized redness were observed. With leukocytosis, eosinophilia and lymphadenopathy, the patient was diagnosed with drug-induced hypersensitivity syndrome.
The patient was admitted to the hospital, received steroid pulse therapy and subsequently recovered.
Reactivation of HHV-6 was checked with paired serum. Drug lymphocyte stimulation test (DLST) of fluconazole was conducted several times during treatment and was negative for all.</td></tr>
<tr><td></td><td colspan="4">Concomitant medications: none</td></tr>
</table>

3 Nivolumab (genetical recombination)

Brand name (name of company)	Opdivo Intravenous Infusions 20 mg, 100 mg (Ono Pharmaceutical Co., Ltd.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Treatment of unresectable malignant melanoma Treatment of unresectable, advanced, or recurrent non-small cell lung cancer (NSCLC) Treatment of unresectable or metastatic renal cell carcinoma Treatment of relapsed or refractory classical Hodgkin lymphoma Treatment of relapsed or metastatic head and neck cancer

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	Hepatic function disorder, hepatitis, sclerosing cholangitis: Hepatic function disorder, hepatitis, and sclerosing cholangitis accompanied by increased levels of AST (GOT), ALT (GPT), γ-GTP, Al-P, and bilirubin, etc., may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken such as discontinuing administration of this drug.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 1 month (April 2014 to May 2017) Cases related to sclerosing cholangitis: 6 cases (no fatal case) The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 10,000 Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures	
1	Male 50s	Recurrent NSCLC (with metastasis to lymph nodes, metastasis to adrenal gland, metastasis to muscles, metastasis to pelvis, and smoking history)	3mg/kg 11 courses at a 2-week interval for each	Sclerosing cholangitis Prior chemotherapy: Combination therapy of cisplatin and pemetrexed was performed for 6 courses.	
				Day 1 of administration:	Nivolumab was administered 3 mg/kg/day in the patient with unresectable advanced and recurrent NSCLC in PS1 (histology : adenocarcinoma, stage 4, TNM stage : T2aN2M1b (the names of organs metastasized : Left adrenal gland, right adductor magnus muscle, left supraspinatus, pelvis)
				Day of discontinuation	The patient received the 11th dose of nivolumab (final administration).
				14 days after discontinuation	Hepatic dysfunction was observed, which resulted in the patient's hospitalization for the treatment. A clinical manifestation (epigastric pain) was observed and liver function tests revealed elevations in AST, ALT, γ-GTP and ALP. A drug-induced liver injury by this drug was suspected. This drug was discontinued and the patient was to receive glycyrrhizin/glycin/DL-methionine combination drug orally 6 tablets/day for a week for follow up.

				Date unknown	Sclerosing cholangitis was found. A clinical manifestation (right upper quadrant pain) was observed.
				20 days after discontinuation	The patient saw the physician with a complaint of pain from epigastrium to the right pneumothorax site. The patient felt tender in the right upper abdomen. Hepatic dysfunction and enhanced inflammatory response were observed. Abdominal ultrasonography (AUS) and CT scan were suggestive of cholecystitis and cholangitis, which led to the patient's emergency hospitalization to the department of gastrointestinal medicine on the same day. The policy was determined to follow up with no surgical interventions. The patient was started on therapy with antibiotics under a fasted condition. AUS findings: Dilation was observed from common bile duct (CBD) to intrahepatic bile duct. No metastases to liver. Gallbladder enlargement was observed. Abdominal CT findings: Edematous wall thickening and biliary dilatation were found in the liver and intrahepatic bile duct. Gallbladder enlargement and dilation from CBD to intrahepatic bile duct were observed. Acute cholangitis was observed. ERCP (endoscopic retrograde cholangiopancreatography) findings: No gallstones observed. Biliary sludge only was observed. EST (endoscopic sphincterotomy) was conducted and completed. EUS (endoscopic ultrasonography) finding: Mild pancreatitis Biliary wall thickening was found. Swelling was detected inside the bile duct with no gallstones. IDUS (intraductal ultrasound) finding: Biliary wall thickening was observed. Bile cytodiagnosis findings: No abnormality
				23 days after discontinuation	HBV-DNA was negative.
				27 days after discontinuation	Hepatic dysfunction and sclerosing cholangitis were improving.
				29 days after discontinuation	Hepatic dysfunction and sclerosing cholangitis aggravated again. ERCP did not find any obstructions. Contrast CT finding was the same as the one at admission. Only mild dilation was observed in CBD and intrahepatic bile duct. HBs-Ag (-). HCV antibody (-). HBs antibody (+). HBc antibody (+).
				35 days after discontinuation	Sclerosing cholangitis induced by nivolumab was suspected. Drip infusion of methylprednisolone sodium succinate (mPSL) (125 mg/day) was started.
				36 days after discontinuation	Auto-antibody test was conducted. Antinuclear antibody (ANA): <40X, myeloperoxidase-antineutrophil cytoplasmic antibody (P-ANCA): <1.0.

				37 days after discontinuation	Administration of mPSL (125 mg/day) was terminated.
				38 days after discontinuation	There was marked improvement in hepatic dysfunction and sclerosing cholangitis. The medication was switched to oral prednisolone (PSL) (30 mg/day) and the patient was discharged from the hospital on the same day.
				42 days after discontinuation	Drip infusion of mPSL (125 mL/day) was started as hepatic dysfunction and sclerosing cholangitis worsened again. Oral administration of mPSL (30 mg/day) was terminated.
				44 days after discontinuation	Administration of mPSL (125 mg/day) was terminated.
				45 days after discontinuation	Little improvement was observed in hepatic dysfunction and sclerosing cholangitis. The treatment was switched to oral PSL (30 mg/day).
				47 days after discontinuation	Oral administration of mPSL (30 mg/day) was terminated.
				48 days after discontinuation	The patient was admitted to the Department of Respiratory Medicine on the day. Contrast CT showed residual cholangitis manifestations (biliary wall thickening, biliary dilatation). They were diagnosed as sclerosing cholangitis in consultation with the department of gastrointestinal medicine. Drip infusion of mPSL (125 mg/day) and treatment with mycophenolate mofetil (MMF) (1g, twice daily) were started.
				58 days after discontinuation	MRCP (magnetic resonance cholangiopancreatography) findings: Mild dilatation of CBD. No abnormality was observed in intrahepatic bile duct.
				62 days after discontinuation	Hepatic dysfunction resolved.
				66 days after discontinuation	The treatment was switched to PSL (100 mg/day) + MMF (1g, twice daily) and started. The dose of PSL was tapered off subsequently.
				88 days after discontinuation	The dose of PSL was reduced to 35 mg/day. Sclerosing cholangitis improved.

Laboratory Examination

Day of examination	Day 1 of administration	14 days after discontinuation	20 days after discontinuation	27 days after discontinuation	29 days after discontinuation	36 days after discontinuation	38 days after discontinuation	42 days after discontinuation
ALP (IU/L)	290	893	1,328	1,557	3,473	2,474	1,871	1,974
γ-GTP (IU/L)	29	265	448	622	1,251	825	624	762
AST (IU/L)	15	210	64	58	687	36	34	274
ALT (IU/L)	13	227	245	100	536	127	83	174
T-Bil (mg/dL)	0.3	0.4	0.3	0.3	0.8	0.3	0.3	0.3
WBC (10,000/μL)	0.74	0.98	1.11	1.10	0.76	0.51	1.12	1.15
CRP (mg/dL)	1.38	8.8	14.05	7.14	6.85	2.96	1.85	3.79
IgG (mg/dL)	–	–	–	–	–	–	–	–

Day of examination	48 days after discontinuation	50 days after discontinuation	55 days after discontinuation	58 days after discontinuation	62 days after discontinuation	69 days after discontinuation	88 days after discontinuation
ALP (IU/L)	4,043	3,069	1,881	2,146	1,449	828	679
γ-GTP (IU/L)	1,457	1,141	874	1,034	708	375	223
AST (IU/L)	236	106	54	69	34	36	23
ALT (IU/L)	953	530	202	276	113	63	30
T-Bil (mg/dL)	1.6	0.9	0.7	0.6	0.3	0.3	0.4
WBC (10,000/μL)	1.85	1.53	1.05	1.24	1.32	0.98	0.88
CRP (mg/dL)	6.94	–	–	2.73	3.14	2.89	5.44
IgG (mg/dL)	–	1,050	849	–	–	–	–

Concomitant medications: lubiprostone, vonoprazan fumarate, loxoprofen sodium hydrate, oxycodone hydrochloride hydrate, acetaminophen

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
2	Female 70s	Metastasis of malignant melanoma to lymph nodes, metastasis to adrenal gland, metastasis to skin, metastasis to liver, liver disorder, autoimmune hepatitis (AIH)	2mg/kg 10 courses at a 3-week interval for each	Sclerosing cholangitis Prior medical intervention : Neck operation, radiotherapy to nose, radiotherapy Day 1 of administration: To treat unresectable malignant melanoma (recurrent, disease type: Mucosal, stage4, no BRAF gene mutations), nivolumab (2 mg/kg/day) was administered. Date unknown AIH worsened, then was controlled with PSL. Day 21 of administration: Elevations in AST and ALT (hepatic function abnormal) (grade 2) were observed. No subjective symptoms. For treatment, the dose of PSL was increased from 7.5 mg to 10 mg. Nivolumab was to be discontinued until the aggravation was relieved to grade 1. Day 22 of administration: AUS revealed the metastasis to liver. Day 47 of administration: The patient received the second dose of nivolumab. Day 48 of administration: AIH did not show any increase in hepatic enzymes after the dose increase of PSL to 10 mg. Day 93 of administration: The patient received the 4th dose of nivolumab. The elevations in AST and ALT improved. Day 114 of administration: The patient received the 5th dose of nivolumab. Day 131 of administration: In the re-examination, CT shows enlarged neck mass, which was PD, but metastasis to liver was SD. Day of discontinuation day The patient received the 10th dose of nivolumab. 22 days after discontinuation Abnormal hepatic function (grade 2) was observed. Differential diagnosis was considered to be necessary for aggravation of AIH and primary disorder, and infections by nivolumab. 23 days after discontinuation AUS was conducted. [AUS findings] Liver: Size, left lobe (normal), right lobe (normal), echo level (normal), liver edge (sharp), surface (fine), internal echo (heterogeneous), presence of mass (+), intrahepatic bile duct dilation (-), CBD dilation (-, 12.9 mm), cysts in the right (-) and in the left (+), portal vein dilation (-), hepatic vein dilation (-). Gallbladder : Enlargement (-), gallstones (-), wall thickness (+, 4.7 mm), coarse wall (-), presence of mass (-). Pancreas: Observed sites (head, body). Enlargement (-), internal echo (homogeneous), echo level (normal), pancreatic duct dilation (-), calcification(-), presence of mass (-).

					[Findings] Liver: A cyst measuring
					AUS was conducted. [AUS findings] Liver: Size, left lobe (normal), right lobe (normal), echo level (normal), liver edge (sharp), surface (fine), internal echo (heterogeneous), presence of mass (+), intrahepatic bile duct dilation (-), CBD dilation (-, 12.9 mm), cysts in the right (-) and in the left (+), portal vein dilation (-), hepatic vein dilation (-). Gallbladder : Enlargement (-), gallstones (-), wall thickening (+, 4.7 mm), coarse wall (-), presence of mass (-). Pancreas: Observed sites (head, body). Enlargement (-), internal echo (homogeneous), echo level (normal), pancreatic duct dilation (-), calcification (-), presence of mass (-). [Findings] Liver: A cyst measuring 26.5×23.3 mm in S4 was found. The metastatic lesion measuring 28.4×35.1 mm in S7 slightly increased in size compared to the same 8 months before. Walls of CBD and gallbladder were edematous with the CBD wall thickened and measured 2.9 mm. Gallbladder wall was thickened to 4.7 mm but its clinical importance was unknown. Inside of the liver was slightly heterogeneous. [Ultrasound diagnosis 1] Chronic liver disorder [Ultrasound diagnosis 2] Gallbladder and CBD wall thickening Abdominal echo showed a chronic liver disorder pattern for hepatic parenchyma. HBs-Ag (-), HCV antibody (-), HA antibody (-), EBV-IgM (-).
				38 days after discontinuation	Sclerosing cholangitis was found. The patient was admitted to the hospital for treatment. The patient was treated with prednisolone sodium succinate injection, PSL, mPSL and MMF. The dose of PSL was increased to 20 mg. The patient was admitted to the hospital for follow up.
				42 days after discontinuation	Abdominal echo was performed. [Finding] (Liver) Some findings were observed. Internal echo: Heterogeneous, coarse. Presence of tumors (+). (Space-occupying lesion (SOL) 1) Located in S8, measuring 35 mm, internal echo: solid, echo level: Hyper, Hypo, shape: nodule. The inside: heterogeneous. (SOL2) Located: The whole, size: 20 mm, internal echo: cystic, No. of tumors: plenty. (Portal vein) No findings. (Pancreas) No findings, the head and body were visualized. (Gallbladder) No findings. (Bile duct) Some findings were observed. CHD was visualized, and wall thickening was measured 3 mm. [Comment] SOL in S8 of the liver increased in size to 38 mm this time. Hump sign was observed. Metastasis was suspected. For the bile duct, wall thickening was observed in the middle of the bile duct. Ultrasound test showed possible bile duct cancer. Lymph node enlargement measuring 25x30 mm was

					observed around the abdominal aortic bifurcation. The patient's medical records were provided from Department of Liver Internal Medicine of C Hospital. [Name of disease] AIH IgG4-related Sclerosing cholangitis was suspected. CBD cancer was suspected. [Symptoms, consultation course and laboratory results] Biliary enzymes were seemingly dominant compared to the time when AIH occurred. Abdominal echo showed wall thickening along the CBD (no such finding observed 7 months before). Differential diagnosis for cholangioma and IgG4-related Sclerosing cholangitis was necessary.
				43 days after discontinuation	Treatment with PSL (20 mg/day) was terminated.
				44 days after discontinuation	MRCP was conducted. [Findings] MRCP, diffusely-spread wall thickening, the sites of stenosis and dilation were suggestive of IgG4-related disease, primary or secondly Sclerosing cholangitis rather than malignant tumors. Other findings were the same as in the previous CT. [Diagnosis] Diffuse bile duct wall thickness [Comment] Diffuse thickness was observed in the bile duct wall and coarse stenosis broadly spread. IgG4 value was within the normal range (the test was conducted in C Hospital), then the patient was diagnosed with immune-related Sclerosing cholangitis. Treatment with mPSL (1 mg/kg/day (30 mg/day)) was started.
				46 days after discontinuation	The dose of mPSL was increased to 2 mg/kg (75 mg)/day.
				49 days after discontinuation	MMF (2g/day) was additionally administered. The dose of mPSL was reduced to 62.5 mg/day. Steroids were subsequently tapered off.
				51 days after discontinuation	Aspergillus antigen was positive (4.1). Aspergillus pneumonia was observed. Amphotericin B was administered as treatment.
				52 days after discontinuation	The dose of mPSL was reduced to 50 mg/day. As the future policy, the dose was to be reduced to 10 mg/week if no aggravation is observed in the patient's liver function. The dose of MMF was unchanged until steroids can be reduced. Elevation in β-D glucan was observed and micafungin sodium was kept administered. Administration with trimethoprim/sulfamethoxazole was terminated.
				55 days after discontinuation	Values of ALP and γ-GTP seemed to be slightly improved.
				56 days after discontinuation	Treatment with Amphotericin B was started.
				58 days after discontinuation	Elevations in ALP and γ-GTP were observed again. D-Bil was increasing. An

					increase of tumors in size stood out after immuno-suppression treatment, but resuscitation was refused for aggravation of general condition associated with tumors under the policy.
				60 days after discontinuation	The dose of mPSL was reduced to 41.25 mg/day.
				62 days after discontinuation	Sclerosing cholangitis resolved. AUS was conducted. Gallbladder wall thickening and bile duct dilation, which had been previously observed, markedly improved, and returned back to normal. The liver function gradually recovered. PSL was considered to be effective. Mass suspected to be a metastatic tumor in S7 of the liver was slightly bigger. Transaminase value was gradually improving. Elevated bilirubin was observed but it might have been the past peak value which just appeared later. The patient was to be followed up. [AUS findings] Liver: Size, left lobe (normal), right lobe (normal), echo level (normal), liver edge (slightly dull) surface (fine), internal echo (heterogeneous), presence of mass (-), intrahepatic bile duct dilation (-), CBD dilation (-, 5.8 mm), cysts in the right (-) and in the left (+), portal vein dilation (-), hepatic vein dilation (-). Gallbladder: Enlargement (-), gallstones (-), wall thickening (-, 3 mm), coarse wall (-), presence of mass (-). Pancreas: Observed sites (head, body, tail) Enlargement (-), internal echo (homogeneous), echo level (normal), pancreatic duct dilation (-), calcification (-), presence of mass (-). Liver: Liver edge was slightly dull with a CH pattern. No remarkable changes in angioma in S3. Metastatic tumor in S7 was slightly bigger than in the previous test. Biliary duct: Previously-observed dilation and wall thickening improved. Gallbladder: Previously-observed wall thickening improved. No other evidently abnormal findings were observed. [Ultrasound diagnosis 1] Metastatic liver tumor [Ultrasound diagnosis 2] Chronic liver disorder Gallbladder wall 3 mm (23 days after discontinuation: 4.7 mm). No biliary dilatation. [Comment] Liver: S3, 25.5×18.9mm, no remarkable changes in cysts. S7, 38.3×34.2mm, metastasized and increased in size. The CBD dilation and wall thickening improved. Liver edge was slightly dull with heterogeneous inside, and CH pattern. Gallbladder: Gallbladder wall thickening markedly improved. Bladder: Collapsed and poor study. γ-GTP, T-Bil decreased while AST, ALT, LDH, ALP and CRP were elevated again. WBC leveled off with no increase in eosinophils. The patient was afebrile.
				66 days after discontinuation	The dose of mPSL was reduced to 30 mg/day.

				72 days after discontinuation	Administration of mPSL (30 mg/day) was terminated.
				73 days after discontinuation	Administration of prednisolone sodium succinate injection (17 mg/day) was started.
				75 days after discontinuation	The body temperature rose to 39 degrees Celsius (negative for blood culture). Treatment with meropenem hydrate was started.
				78 days after discontinuation	Treatment with meropenem hydrate and MMF (2g/day) was terminated. Due to difficulty for oral medications and refusal of injection and blood sampling, amphotericin B was discontinued.
				79 days after discontinuation	Prednisolone sodium succinate injection (17 mg/day) was terminated.
				80 days after discontinuation	Body temperature of 39 degrees Celsius, hypotension, an infiltrative shadow and fungus ball in the right lung with thoracic imaging were observed and diagnosed as pulmonary aspergillosis. Administration of amphotericin B was restarted for pain relief when the patient was febrile.
				84 days after discontinuation	Body temperature did not go back to normal. The patient was treated with acetaminophen and fentanyl. Amphotericin B was terminated.
				87 days after discontinuation	The patient died of pulmonary aspergillosis, malignant melanoma.

Laboratory Examination

Day of examination	Day 1 of administration:	Day 21 of administration:	Day 47 of administration:	Day 38 of administration:	Day 44 of administration:	Day 55 of administration:	Day 58 of administration:	Day 62 of administration:	Day 75 of administration:
ALP (IU/L)	134	167	174	601	854	760	819	963	1,422
γ-GTP (IU/L)	27	52	64	381	596	803	858	786	635
AST (IU/L)	36	109	55	164	384	164	139	181	148
ALT (IU/L)	22	126	57	137	252	146	112	132	90
T-Bil (mg/dL)	0.49	0.51	0.50	1.04	0.80	1.21	1.83	1.62	0.98
WBC (10,000/μL)	–	–	–	1.336	1.584	1.534	1.736	1.593	1.861
CRP (mg/dL)	–	–	–	10.61	5.99	4.25	4.51	9.63	8.58

Concomitant medications: prednisolone, acetaminophen

3

Revision of Precautions (No. 286)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs in accordance with the Notifications dated July 4, 2017

1

Analgesics, anti-itchings, astringents, anti-inflammatory agents (prescription drugs)

Loxoprofen sodium hydrate (dermatologic preparation)

Brand name	Loxonin Pap 100 mg, Loxonin Tape 50 mg, 100 mg (Lead Chemical Co., Ltd.), Loxonin Gel 1% (Daiichi Sankyo Co., Ltd.), Loxoprofen Na Spray 1% YD (Yoshindo Inc.), and others
Adverse reactions (clinically significant adverse reactions)	Shock, anaphylaxis: Shock or anaphylaxis (decreased blood pressure, urticaria, laryngeal oedema, dyspnoea, etc.) may occur. Patients should be carefully monitored. If any abnormalities are observed, use of this drug should be discontinued immediately and appropriate measures should be taken.

2

Anti-inflammatory agents (guidance-mandatory drugs)

Loxoprofen sodium hydrate (dermatologic preparation)

Brand name	Loxonin S Poultice, Loxonin S Tape, Loxonin S Tape L (Lead Chemical Co., Ltd.), Loxonin S Gel (Daiichi Sankyo Healthcare Co., Ltd.)
Consultation	If the following symptoms are observed after taking this drug, these may be adverse reactions, so immediately discontinue the use of this drug, and show this document to your physician or pharmacist for a consultation. The following serious symptoms occur in rare cases. In such a case, immediately seek medical aid. Shock (anaphylaxis): Symptoms, such as itching of skin, urticaria, hoarseness, sneezing, itchy throat, breathing difficulties, palpitations, and clouding of consciousness may occur immediately after use.

3

Antidotes

Hydroxocobalamin

Brand name	Cyanokit for Injection 5 g Set
Adverse reactions (clinically significant adverse reactions)	Acute kidney injury: Acute kidney injury may occur, and cases with renal tubular necrosis have also been reported. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.

4 **Antineoplastics-Miscellaneous**

Nivolumab (genetical recombination)

Brand name	Opdivo Intravenous Infusions 20 mg, 100 mg (Ono Pharmaceutical Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	Hepatic function disorder, hepatitis, sclerosing cholangitis: Hepatic function disorder, hepatitis, and sclerosing cholangitis accompanied by increased levels of AST (GOT), ALT (GPT), γ-GTP, Al-P, and bilirubin, etc., may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken such as discontinuing administration of this drug.

5 **Chemotherapeutics-Miscellaneous**

a. Fluconazole
b. Fosfluconazole

Brand name	a. Diflucan Capsules 50 mg, 100 mg, Diflucan Dry Syrup 350 mg, 1400 mg, Diflucan Intravenous Solution 50 mg, 100 mg, 200 mg (Pfizer Japan Inc.), and others b. Prodif Intravenous Solution 100 mg, 200 mg, 400 mg (Pfizer Japan Inc.)
Adverse reactions (clinically significant adverse reactions)	Drug-induced hypersensitivity syndrome: Initial symptoms of pyrexia and rash, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic function disorder, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken. Symptoms are often accompanied by virus reactivation such as human herpes virus type 6 (HHV-6). Caution should be exercised against recurrence or prolongation of rash, pyrexia, and hepatic function disorder, etc. that may occur even after discontinuation of administration.

6 **Diagnostic Agents-Miscellaneous**

Patch test products containing gold (I) sodium thiosulfate

Brand name	Patch Test Panel (S) (Sato Pharmaceutical Co., Ltd.)
Important Precautions	Late positive reactions may occur 7 to 10 days after the test. With gold (I) sodium thiosulfate, there have been reports of a late positive reaction occurring as late as 20 days or more after the test. Before performing the patch test, patients should be informed that sensitization or late positive reactions may occur, and be instructed to visit a medical institution immediately if positive reactions occur after the test result is determined.

7 **Antipyretics and analgesics, anti-inflammatory agents**

Tramadol hydrochloride (oral dosage form)

Brand name	Tramal OD Tablets 25mg, 50mg, Onetram Tablets 100mg (Nippon Shinyaku Co., Ltd.)
Important Precautions	This drug should not be used in children younger than 12 years old because serious respiratory depression may occur (see Pediatric Use). This drug should not be used in patients younger than 18 years old who are obese or have obstructive sleep apnoea syndrome or serious lung disease because the risk of serious respiratory depression may increase.
Pediatric Use	The safety of this drug in children 12 years old and older has not been established (no clinical experience). This drug should not be used in children younger than 12 years old (Overseas there have been reports that the risk of serious respiratory depression, including death, is high in children younger than 12 years old).

8 **Antipyretics and analgesics, anti-inflammatory agents**

Tramadol hydrochloride (injectable dosage form)

Brand name	Tramal Injection 100 (Nippon Shinyaku Co., Ltd.)
Important Precautions	This drug should not be used in children younger than 12 years old because serious respiratory depression may occur (see Pediatric Use). This drug should not be used in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy because the risk of serious respiratory depression may increase. This drug should not be used in patients younger than 18 years old who are obese or have obstructive sleep apnoea syndrome or serious lung disease because the risk of serious respiratory depression may increase.
Pediatric Use	The use of this drug in children 12 years old and older is not recommended because the safety of this drug has not been established (no clinical experience). This drug should not be used in children younger than 12 years old (Overseas there have been reports that the risk of serious respiratory depression, including death, is high in children younger than 12 years old.)

9

Antipyretics and analgesics, anti-inflammatory agents

Tramadol hydrochloride/Acetaminophen

Brand name	Tramcet Combination Tablets (Janssen Pharmaceutical K.K.)
Important Precautions	This drug should not be used in children younger than 12 years old because serious respiratory depression may occur (see Pediatric Use). This drug should not be used in patients younger than 18 years old who are obese or have obstructive sleep apnoea syndrome or serious lung disease because the risk of serious respiratory depression may increase.
Pediatric Use	The safety of this drug in children 12 years old and older has not been established. This drug should not be used in children younger than 12 years old (Overseas there have been reports that the risk of serious respiratory depression, including death, is high in children younger than 12 years old).

10

Antitussives (prescription drugs)

Dihydrocodeine phosphate/*dl*-Methylephedrine hydrochloride/Chlorpheniramine maleate

Brand name	Lightgen Combination Syrup, Huscode Combination Tablets, Nichicode Combination Powder, and others (Teijin Pharma Ltd., and others)
Careful Administration	Geriatrics, patients with debility (Adverse reactions may occur because metabolic and excretory functions are decreased in geriatrics and patients with debility [see Geriatric Use]).
Important Precautions	This drug should not be used in children younger than 12 years old because serious respiratory depression may occur (see Pediatric Use). This drug should not be used in patients younger than 18 years old who are obese or have obstructive sleep apnoea syndrome or serious lung disease because the risk of serious respiratory depression may increase.
Pediatric Use	This drug should not be used in children younger than 12 years old (They are highly susceptible to respiratory depression. Overseas there have been reports that the risk of serious respiratory depression, including death, is high in children younger than 12 years old).

11 **Antitussives (prescription drugs)**

Diprophylline/Dihydrocodeine phosphate/*dl*-Methylephedrine hydrochloride/ Diphenhydramine salicylate/Acetaminophen/Bromovelerylurea

Brand name Coughcode-N Combination Tablets (Pfizer Japan Inc.)

Careful Administration Children 12 years old and older (See Pediatric Use)
If patients do not adequately respond to this drug even when used properly according to the dosage and administration, this drug may not be appropriate. Administration should be discontinued. When administering to children 12 years old and older, patients should be instructed for proper use and be carefully followed up.

Important Precautions This drug should not be used in children younger than 12 years old because serious respiratory depression may occur (see Pediatric Use).
This drug should not be used in patients younger than 18 years old who are obese or have obstructive sleep apnoea syndrome or serious lung disease because the risk of serious respiratory depression may increase.

Pediatric Use Children 12 years old and older should be monitored carefully particularly for adverse reactions. Careful administration is required such as limiting to the minimum dose required. (They are highly susceptible to respiratory depression. Safety in children has not been established.)

This drug should not be used in children younger than 12 years old (They are highly susceptible to respiratory depression. Overseas there have been reports that the risk of serious respiratory depression, including death, is high in children younger than 12 years old).

12 **Antitussives and expectorants (prescription drugs)**

a. Platycodon fluidextract/Glycyrrhiza extract/Plantago herb extract/Peony root extract/Dihydrocodeine phosphate

b. Codeine phosphate hydrate/Cherry bark extract

Brand name a. Opisezol Codeine Solution (Nichi-Iko Pharmaceutical Co., Ltd.)
b. Salipara-Codeine Solution (Maruishi Pharmaceutical Co., Ltd.)

Important Precautions This drug should not be used in children younger than 12 years old because serious respiratory depression may occur (see Pediatric Use).
This drug should not be used in patients younger than 18 years old who are obese or have obstructive sleep apnoea syndrome or serious lung disease because the risk of serious respiratory depression may increase.

Pediatric Use This drug should not be used in children younger than 12 years old (They are highly susceptible to respiratory depression. Overseas there have been reports that the risk of serious respiratory depression, including death, is high in children younger than 12 years old).

13 **Antitussives and expectorants, opium alkaloids (prescription drugs)**

a. Codeine phosphate hydrate
b. Dihydrocodeine phosphate

Brand name

a. Codeine Phosphate Powder 1% “Takeda”, Codeine Phosphate Tablets 5mg “Sioe”, Codeine Phosphate Tablets 20mg “Takeda”, and others (Daiichi Sankyo Co., Ltd., Sioe Pharmaceutical Co., Ltd., and others)
b. Dihydrocodeine Phosphate Powder 1% “Daiichi Sankyo”, Dihydrocodeine Phosphate Powder 10% “Daiichi Sankyo”, Dihydrocodeine Phosphate Powder “Daiichi Sankyo”, and others (Daiichi Sankyo Co, Ltd., and others)

Important Precautions

This drug should not be used in children younger than 12 years old because serious respiratory depression may occur (see Pediatric Use). This drug should not be used in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy because the risk of serious respiratory depression may increase. This drug should not be used in patients younger than 18 years old who are obese or have obstructive sleep apnea syndrome or serious lung disease because the risk of serious respiratory depression may increase.

Pediatric Use

This drug should not be used in children younger than 12 years old (They are highly susceptible to respiratory depression. Overseas there have been reports that the risk of serious respiratory depression, including death, is high in children younger than 12 years old).

14 **Antitussives and expectorants (prescription drugs)**

Dihydrocodeine phosphate/Ephedrine hydrochloride/ Ammonium chloride

Brand name

Sekicode Combination Syrup (Nichi-Iko Pharmaceutical Co., Ltd.)

Important Precautions

If patients do not adequately respond to this drug even when used properly according to the dosage and administration, this drug may not be appropriate.
Administration should be discontinued. When administering to children 12 years old and older, patients should be instructed for proper use and be carefully followed up.
This drug should not be used in children younger than 12 years old because serious respiratory depression may occur (see Pediatric Use). This drug should not be used in patients younger than 18 years old who are obese or have obstructive sleep apnoea syndrome or serious lung disease because the risk of serious respiratory depression may increase.

Pediatric Use

This drug should not be used in children younger than 12 years old (They are highly susceptible to respiratory depression. Overseas there have been reports that the risk of serious respiratory depression, including death, is high in children younger than 12 years old.)

15

Common cold drugs, Antitussive and Expectorant (OTC drugs)

Products containing codeine phosphate hydrate and products containing dihydrocodeine phosphate (preparations with the administration for patients younger than 2 years old)

Brand name	Pabron Gold A, and others (Taisho Pharmaceuticals Co., Ltd., and others)
Consultation	The following persons should contact a physician, pharmacist, or registered salesperson for a consultation before administration. Persons diagnosed as follows: Respiratory functional disorder, obstructive sleep apnoea syndrome, obesity If the following symptoms are observed after taking this drug, these may be adverse reactions, so immediately discontinue the use of this drug, and show this document to your physician, pharmacist, or registered salesperson for a consultation. The following serious symptoms occur in rare cases. In such a case, immediately seek medical aid. Respiratory depression: Symptoms such as shortness of breath and difficulty in breathing may occur.
Precautions of Dosage and Administration	For children younger than 12 years old, examination by a physician should always precede administration of this drug.

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Common cold drugs, Antitussive and Expectorant (OTC drugs)

Products containing codeine phosphate hydrate and products containing dihydrocodeine phosphate (preparations with the administration for patients younger than 12 years old and without the administration for patients younger than 2 years old)

Brand name	Shin Lulu A Tablets s, and others (Daiichi Sankyo Healthcare Co., Ltd., and others)
Consultation	The following persons should contact a physician, pharmacist, or registered salesperson for a consultation before administration. Persons diagnosed as follows: Respiratory functional disorder, obstructive sleep apnoea syndrome, obesity If the following symptoms are observed after taking this drug, these may be adverse reactions, so immediately discontinue the use of this drug, and show this document to your physician, pharmacist, or registered salesperson for a consultation. The following serious symptoms occur in rare cases. In such a case, immediately seek medical aid. Respiratory depression: Symptoms such as shortness of breath and difficulty in breathing may occur.
Precautions of Dosage and Administration	For children younger than 12 years old, examination by a physician should always precede administration of this drug.

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Common cold drugs, Antitussive and Expectorant (OTC drugs)

Products containing codeine phosphate hydrate and products containing dihydrocodeine phosphate (preparations without the administration for patients younger than 12 years old)

Brand name	Benza Block L, and others (Takeda Consumer Healthcare Co., Ltd., and others)
Consultation	The following persons should contact a physician, pharmacist, or registered salesperson for a consultation before administration. Persons diagnosed as follows: Respiratory functional disorder, obstructive sleep apnoea syndrome, obesity If the following symptoms are observed after taking this drug, these may be adverse reactions, so immediately discontinue the use of this drug, and show this document to your physician, pharmacist, or registered salesperson for a consultation. The following serious symptoms occur in rare cases. In such a case, immediately seek medical aid. Respiratory depression: Symptoms such as shortness of breath and difficulty in breathing 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 new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing authorization holder (MAH) is responsible for collecting ADR from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of June 30, 2017)
◎: Products for which EPPV was initiated after May 1, 2017

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Hydromorphone Hydrochloride Narurapid Tablets 1 mg, 2 mg, 4 mg, Narusus Tablets 2 mg, 6 mg, 12 mg, 24 mg	Daiichi Sankyo Propharma Co., Ltd.	June 19, 2017
◎	Naldemedine Tosilate Symproic Tablets 0.2 mg	Shionogi & Co., Ltd.	June 7, 2017
	Aflibercept Beta (Genetical Recombination) Zaltrap 100 mg I.V. Infusion, 200 mg I.V. Infusion	Sanofi K.K.	May 29, 2017
	Guanfacine Hydrochloride Intuniv Tablets 1 mg, 3 mg	Shionogi & Co., Ltd.	May 26, 2017
	Forodesine Mundesine Capsule 100 mg	Mundipharma K.K.	May 24, 2017
	Ixazomib Citrate Ninlaro capsules 2.3 mg, 3 mg, 4 mg	Takeda Pharmaceutical Company Limited	May 24, 2017
	Ustekinumab (Genetical Recombination) *1 (1) Stelara Intravenous Infusion 130 mg, (2) Stelara Subcutaneous Injection 45 mg Syringe	Janssen Pharmaceutical K.K.	May 24, 2017
	Drospirenone/Ethinylestradiol Betadex*2 YazFlex Combination Tablets	Bayer Yakuhin, Ltd.	April 21, 2017
	Golimumab (Genetical Recombination)*3 Simponi Subcutaneous Injection 50 mg, 100 mg Syringe	Janssen Pharmaceutical K.K.	March 30, 2017
	Zinc Acetate Dihydrate*4 Nobelzin Capsules 25 mg, 50 mg, Nobelzin Tablets 25 mg, 50 mg	Nobelpharma Co., Ltd.	March 24, 2017
	Omalizumab (Genetical Recombination)*5 Xolair for S.C. Injection 75 mg, 150 mg	Novartis Pharma K.K.	March 24, 2017
	Linaclotide Linzess Tablets 0.25 mg	Astellas Pharma Inc.	March 22, 2017
	Artemether/Lumefantrine Riamet Combination Tablets	Novartis Pharma K.K.	March 7, 2017
	Triamcinolone Acetonide	Wakamoto Co., Ltd.	March 2, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	MaQaid Intravitreal Injection 40 mg		
	Choriogonadotropin Alfa (Genetical Recombination) Ovidrel Syringe 250 μg	Merck Serono Co., Ltd.	March 1, 2017
	Apremilast Otezla Tablets 10 mg, 20 mg, 30 mg	Celgene K.K.	March 1, 2017
	Dimethyl Fumarate Tecfidera Capsules 120 mg, 240 mg	Biogen Japan Ltd.	February 22, 2017
	Plerixafor Mozobil Subcutaneous Injection 24 mg	Sanofi K.K.	February 22, 2017
	Tenofovir Alafenamide Fumarate Vemlidy Tablets 25 mg	Gilead sciences K.K.	February 15, 2017
	Daclatasvir Hydrochloride / Asunaprevir / Beclabuvir Hydrochloride Ximency Combination Tablets	Bristol-Myers Squibb K.K.	February 15, 2017
	Etelcalcetide Hydrochloride Parsabiv Intravenous Injection for Dialysis 2.5 mg, 5 mg, 10 mg	ONO Pharmaceutical Co., Ltd.	February 15, 2017
	Pembrolizumab (Genetical Recombination) Keytruda Injection 20 mg, 100 mg[*6]	MSD K.K.	February 15, 2017
	Pembrolizumab (Genetical Recombination) Keytruda Injection 20 mg, 100 mg[*7]	MSD K.K.	February 15, 2017
	Ticagrelor Brilinta Tablets 60 mg, 90 mg	AstraZeneca K.K.	February 8, 2017
	EmtricitabineTenofovirAlafenamide Fumarate Descovy Combination Tablets LT and HT	Japan Tobacco Inc.	January 27, 2017
	DarunavirEthanolate/Cobicistat Prezcobix Combination Tablets	Janssen Pharmaceutical K.K.	January 4, 2017

*1 (1) Induction therapy for moderate to severe active crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments),
(2) maintenance therapy for moderate to severe active crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments)

*2 Improvement of pain in endometriosis, dysmenorrhoea

*3 Improvement and maintenance for moderate to severe ulcerative colitis (for use only in patients who have not sufficiently responded to conventional treatments)

*4 Hypozincemia

*5 Idiopathic chronic urticaria (limited to patients who are not adequately responsive to conventional treatments)

*6 PD-L1-positive, unresectable, advanced or relapsed NSCLC

*7 Radically unresectable malignant melanoma

*8 Familial mediterranean fever, Tumour necrosis factor receptor-associated periodic syndrome, Mevalonate kinase deficiency/Hyper IgD syndrome

*9 Chronic cardiac failure

*10 Improvement of pain in adenomyosis uteri