Pharmaceuticals and Medical Devices Safety Information

No. 362 April 2019

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only in Japanese).

Available information is listed here

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Register here

Published by
Ministry of Health, Labour and Welfare

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Pharmaceuticals and Medical Devices Safety Information

No. 362 April 2019

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Guidelines for Prescription Drug Marketing Information Provision**		The MHLW in response to the recent grave violative advertising of prescription drugs in the form of false or exaggerated advertisement has been working on a Surveillance Monitoring Project for Prescription Drug Advertising since Fiscal Year (FY) 2016. In order to address the issues involved in advertising regulations acknowledged in the course of the project, the Guidelines for Prescription Drug Marketing Information Provision were established on September 25, 2018. This section will introduce the background and outline of the guidelines.	4
2	**Revision of Package Inserts of Intravenous Injection Products Containing Sorbitol or Fructose as Excipient for Use in Patients with Hereditary Fructose Intolerance**		In October 2017, the European Medicines Agency (EMA) revised the guideline on Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use, which states that intravenous injection products containing sorbitol or fructose as an excipient are contraindicated for use in patients with hereditary fructose intolerance (HFI). In line with this measure by the EMA, precautions in the relevant Japanese package inserts were revised as well. This section will outline the revision of the package insert.	9
3	**Important Safety Information**	*P* *C*	Baloxavir marboxil (and 2 others): Regarding the revision of the precautions in package inserts of drugs in accordance with the Notification dated March 1 and 19, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.	13
4	**Revision of Precautions (No. 302)**	*P*	Oseltamivir phosphate (and 7 others)	29
5	**List of Products Subject to Early Post-marketing Phase Vigilance**		List of products subject to Early Post-marketing Phase Vigilance as of February 28, 2019.	32

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries

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

If providers of medical care and pharmaceutical products 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 providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse Drug Reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CK	Creatine kinase
CRP	C-reactive protein
CT	Computed tomography
DLST	Drug-induced lymphocyte stimulation test
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
GL	Guidelines
Hb	Hemoglobin
JPMA	Japan Pharmaceutical Manufacturers Association
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MR	Medical representative
MRI	Magnetic resonance imaging
MSL	Medical science liaison
NEU	Neutrophil
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
RBC	Red blood cell
SJS	Stevens-Johnson Syndrome
TEN	Toxic epidermal necrolysis
WBC	White blood cell

1

Guidelines for Prescription Drug Marketing Information Provision

1. Current Status of Regulations on Advertising of Drugs etc.

In recent years, there have been violative advertising of prescription drugs, including false and exaggerated statements, which cannot be overlooked, and such incidents have made a significant impact not only in the clinical setting but also on society overall.

[1] Responses to these incidents

- Responses of the Japan Pharmaceutical Manufacturers Association (JPMA)

Full revision of the Guidelines for Advertising of Prescription Drugs in September 2015
Introduction of an advertising review system by external third parties

- Responses of the Ministry of Health, Labour and Welfare (MHLW)

The MHLW established a Review Committee for a Proper System for Clinical Research in April 2014, and the health and labour sciences research group released Proposals for Review of Proper Advertising of Prescription Drugs in November 2014 on the proper advertising for prescription drugs.

[2] Surveillance Monitoring Project for Prescription Drug Advertising

Based on the proposals by the study group, the MHLW has been working on a Surveillance Monitoring Project for Prescription Drug Advertising" since Fiscal Year (FY) 2016.

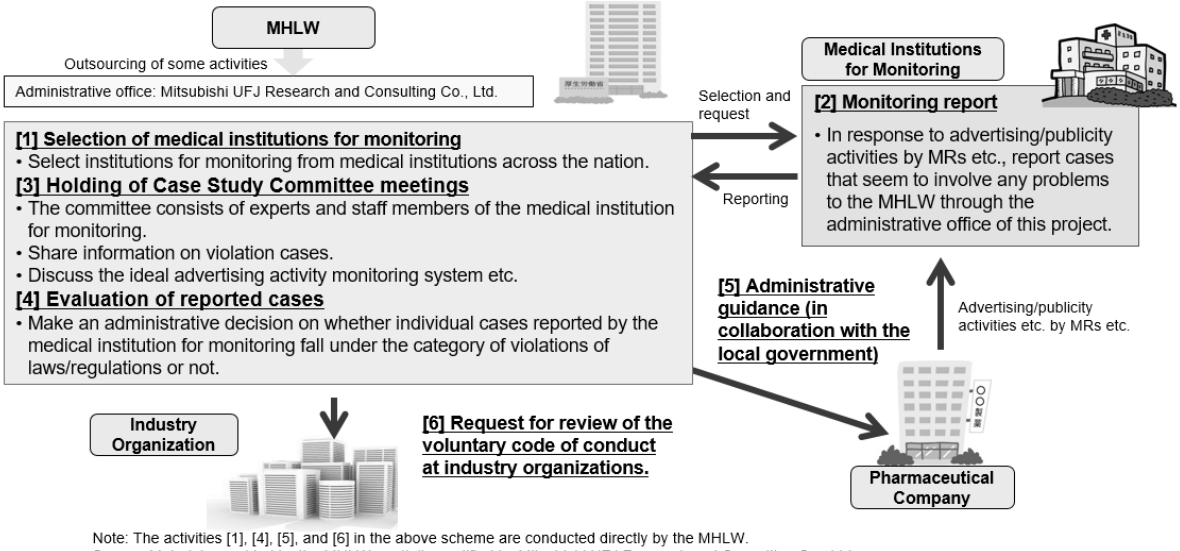
2. Surveillance Monitoring Project for Prescription Drug Advertising [Summary, FY2017]

(1) Purpose of the Project

The purpose of this project is to ensure proper pharmaceutical advertising by pharmaceutical companies by achieving early detection of acts that fall under the category of violative advertising and facilitating the implementation of the necessary actions, including administrative guidance, as well as encouraging voluntary efforts of pharmaceutical companies, industry organizations, etc.

(2) Summary of the Project

- Based on the following scheme, a monitoring survey on advertising/publicity by MRs, MSL, etc., and a survey in specialty/academic journals for healthcare professionals, websites of pharmaceutical companies, and information sites for healthcare professionals were conducted.
- The duration of the survey was 5 months in FY2017.



Note: The activities [1], [4], [5], and [6] in the above scheme are conducted directly by the MHLW.
Source: Materials provided by the MHLW, partially modified by Mitsubishi UFJ Research and Consulting Co., Ltd.

(3) Summary of Project Results

- During the 5-month period in FY2017, **reports on suspected cases concerning the appropriateness of advertising for a total of 52 drug cases etc., were accumulated, and 67 cases of suspected violations** were found. (None of them were considered to be clearly subject to immediate control from the standpoint of the seriousness of the health injury, the maliciousness of the case, etc.)
- Frequently reported suspected violations were "use of expressions that could cause a misunderstanding of the facts" (41.8%), "data processing that could cause a misunderstanding of the facts" (14.9%), and "presentation of unapproved indications or dosage and administration" (11.9%).
- The most frequent routes of obtaining information on drugs etc. reported as suspected violations were "corporate product briefing sessions" (34.6%), followed by "pharmaceutical companies' personnel (verbal explanations)" (30.8%), "pharmaceutical companies' personnel (handouts/supplies)" (28.8%), and "corporate websites" (15.4%).

[Suspected Violations (Multiple answers were allowed.)] (Unit: Case)

Suspected violation	No. of cases	Percentage of total number of reports
Presentation of unapproved indications or dosage and administration	8	11.9%
Data processing that could cause a misunderstanding of the facts	10	14.9%
Use of expressions that could cause a misunderstanding of the facts	28	41.8%
Use of unreliable data	6	9.0%
Underestimation of safety	5	7.5%
Not clearly stating conflicts of interest	0	0.0%
Use of expressions that disparage the products of other companies	3	4.5%
Others	7	10.4%

* Suspected violations are based on reports by monitoring institutions etc.
* The percentage of the total number of reports was calculated using the total number of cases of suspected violations (67 cases) as the denominator.

2. Issues Involved in Regulations on Advertising of Drugs etc.

Issues involved in advertising regulations were reconfirmed through the Surveillance Monitoring Project for Prescription Drug Advertising.

A. Cases in which it is less likely to leave evidence (common to all of Articles 66, 67, and 68, Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics [PMD Act.])

A number of cases have been reported through the advertising surveillance monitoring, in which the materials basically used for the advertisings are appropriate, but the explanations given verbally or only using video images on the mobile computers of medical representatives (MRs) are inappropriate, but in these cases, evidence of the explanations is hardly available.

[Specific examples]

Verbal explanation given on an individual basis, explanation given only using video images on the MR's mobile computer, explanation using slides at a product briefing session, etc.

[Issue]

To provide guidance on violation cases, it is necessary to confirm the fact, including evidence, and business operators should take further efforts, in conjunction with administrative actions, to prevent such occurrences.

B. Cases in which the statement does not amount to a false or exaggerated claim, but is considered to be encouraging improper use (Article 66, PMD Act.)

Although a voluntary code of conduct has been established for each industry in Japan, inappropriate cases have been detected through the advertising surveillance monitoring.

[Issue]

These inappropriate cases may adversely affect decisions on the proper use of drugs by healthcare professionals, and business operators should take further efforts, in conjunction with administrative actions, to prevent such occurrences.

C. Cases in which it is difficult to decide whether the employed approaches constitute an advertisement under the PMD Act (common to all of Articles 66, 67, and 68, PMD Act.)

There has been an increase in approaches that it is difficult to decide whether they constitute an advertisement under the PMD Act, such as affiliate advertising (result-reward advertising.)*

[Specific examples]

Verbal explanation given on an individual basis, advertising using research papers and articles, affiliated advertising, advertising to spread awareness of diseases, etc.

[Issue]

If the involvement of a corporate side is confirmed, the three requirements to be considered as advertising are satisfied for all of the above cases; however, it is not easy to confirm the involvement of a corporation.

As for information provision activities that do not fall under the category of advertising, but may lead to improper use, business operators should take further efforts, in conjunction with administrative actions, to prevent such occurrences.

D. Ensuring of information provision to healthcare professionals and patients

Advertising of unapproved drugs or off-label use of drugs is prohibited under Article 68 of the PMD Act; however, provision of published articles etc. by corporations does not fall under the category of advertising in some cases if use of the unapproved drugs is required for specific patients. Therefore, there is room to consider the proper information provision when encountering such a case.

[Issue]

There are cases in which physicians and other healthcare professionals, as well as patients may request corporations to provide published articles of overseas off-label use for reference because of medical needs. It is therefore required to make assessment to organize the guidelines for information provision of off-label use of drugs in Japan in reference to US guidelines.

3. Guidelines for Prescription Drug Marketing Information Provision

To address these issues involved in advertising regulations, the Guidelines for Prescription Drug Marketing Information Provision were established in 2018 (PSEHB Notification No. 0925-1 by the Director General of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated September 25, 2018).

[1] Purpose:

The purpose of the guideline is to facilitate the proper advertising or any other similar actions involved in the prescription drug marketing information provision and thereby to ensure proper use of drugs and improvement of health and hygiene.

[2] Scope etc.:

- ○ This guideline applies to marketing information provision conducted by marketing authorization holders (MAHs) and their contractors, partner companies, and drug wholesalers.
- ○ “Marketing information provision” comprise the provision of information in the expectation of promoting sales, for example by enhancing recognition of the name or efficacy/safety of a specific prescription drug, regardless of whether it is performed actively or passively.
- ○ “Materials etc. for marketing information provision” are materials and information used for

such activities regardless of method and form of provision, including verbal explanations, video images on computers, and data provided in electromagnetic form.
- ○ This guideline applies to Medical Representatives (MRs), Medical Science Liaison (MSL), and all employees etc., regardless of job title or department.

[3] Basic concept:
- ○ Principles for marketing information provision

[4] Responsibilities of the MAHs etc.
- ○ Responsibilities of the management
- ○ Improvement of the in-house organization
- ○ Ensuring of the appropriateness of materials etc. for marketing information provision
- ○ Evaluation of and education, etc. on marketing information provision
- ○ Instructions for supervision, e.g., monitoring
- ○ Preparation and management of procedures and records
- ○ Handling of inappropriate marketing information provision
- ○ Handling of claims/complaints etc.

[5] Responsibilities of persons involved in marketing information provision activities:
- ○ Efforts for self-improvement
- ○ Prohibition of using materials etc. comprising inappropriate marketing information provision

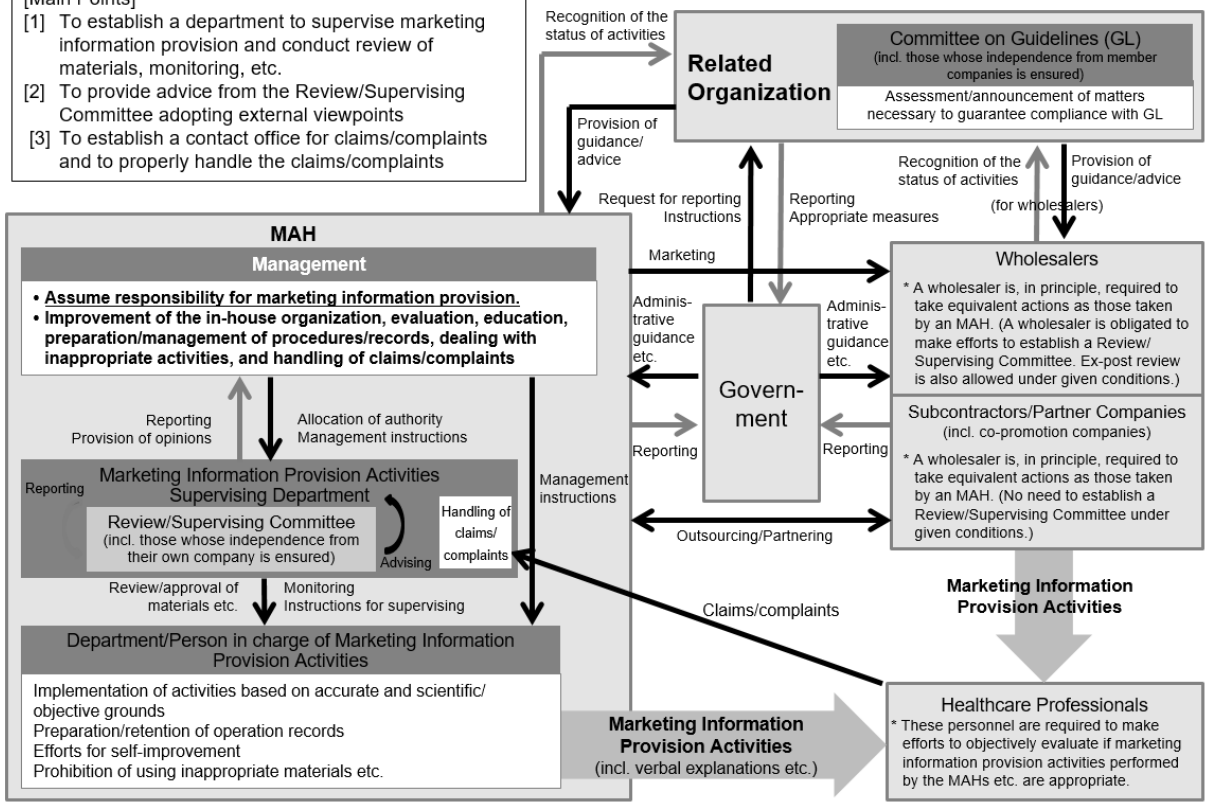
[6] Others:
- ○ Actions at related organizations
- ○ Provision of information on unapproved drugs, off-label use of drugs, etc.
- ○ Exceptions for drug wholesalers
- ○ Responsibilities of healthcare professionals, etc.

[7] Effective date:
- ○ April 1, 2019
- ○ October 1, 2019 for items associated with Chapter II and supervising departments

* For the details of the guidelines, see the MHLW website: https://www.mhlw.go.jp/content/000359881.pdf (Only in Japanese)

Responsibilities and In-house Organization, etc. of Marketing Information Provision

[Main Points]
[1] To establish a department to supervise marketing information provision and conduct review of materials, monitoring, etc.
[2] To provide advice from the Review/Supervising Committee adopting external viewpoints
[3] To establish a contact office for claims/complaints and to properly handle the claims/complaints



2

Revision of Package Inserts of Intravenous Injection Products Containing Sorbitol or Fructose as Excipient for Use in Patients with Hereditary Fructose Intolerance

In October 2017, the European Medicines Agency (EMA) revised the guideline on "Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use," which states that intravenous injection products containing sorbitol or fructose as an excipient are contraindicated for use in patients with hereditary fructose intolerance (HFI). In the package inserts of all intravenous injection products containing sorbitol or fructose as an active ingredient in Japan, HFI patients are already listed under the Contraindications for all of these products. In response to the report of the measure that has been taken overseas, PMDA considered the necessity of revising the package inserts of intravenous injection products containing sorbitol or fructose as an excipient. As a result of investigation while taking the opinions of expert advisors into consideration, it was decided that it is necessary to additionally provide descriptions about HFI patients based on the following points.

- Administration of sorbitol- or fructose-containing intravenous injection products in HFI patients may cause an increased risk of hypoglycaemia, hepatic impairment, renal impairment, etc., and may also lead to a fatal outcome.
- There are actual reported cases of the administration of sorbitol- or fructose-containing intravenous fluids or injections to patients with unknown HFI, some of which resulted in death.
- It is not expected that there will be any ethnic differences in the risk of the administration of sorbitol or fructose to HFI patients.
- There were no confirmed cases of the administration of intravenous injection products containing sorbitol or fructose as an excipient in HFI patients that resulted in a serious outcome.

Based on these assessments, MHLW issued a notification on the instructions for revision of the package inserts of intravenous injection products containing sorbitol or fructose as an excipient as of March 19, 2019, as shown below.

Intravenous injection preparations containing sorbitol as excipient

Patients with hereditary fructose intolerance (fructose, a metabolite produced in the body from D-sorbitol* added to the product as excipient cannot be broken down, which may induce hypoglycaemia, hepatic failure, renal failure, etc.) *“D-sorbitol” here should be replaced with "sorbitol" for products with their current package inserts specifying "sorbitol."

Intravenous injection preparations containing fructose as excipient

Patients with hereditary fructose intolerance (fructose added to the product as excipient cannot be broken down, which may induce hypoglycaemia, hepatic failure, renal failure, etc.)

HFI is a very rare disease; the prevalence of HFI in European Caucasians is estimated to be 1/20 000 to 1/30 000 people, while it is understood that there have been no new literature reports on HFI cases in Japan after five patients in three families had been reported by 1990. From the next page, Dr. Tomohiro Kamoda, Department of Pediatrics, Ibaraki Prefectural Central Hospital, gives an overview of HFI. We would appreciate your understanding of the pathology etc. of HFI and your continued cooperation with the proper use of sorbitol- or fructose-containing intravenous injection products.

(Reference)
Revision of Precautions of the Package Insert of Preparations Containing Sorbitol or Fructose as Excipient (Intravenous Injections) (PSEHB/PSD Notification No. 0319-2, dated March 19, 2019)
https://www.mhlw.go.jp/content/000489809.pdf (only in Japanese)
http://www.pmda.go.jp/files/000228664.pdf (Attachment 1: Sorbitol)
http://www.pmda.go.jp/files/000228665.pdf (Attachment 2: Fructose)

Hereditary Fructose Intolerance

1. Concept/Definition

Hereditary fructose intolerance (HFI) is a genetic disease caused by a deficiency of the liver enzyme aldolase B. Since the enzyme is lacking, metabolism of fructose ingested with meals is blocked leading to accumulation of fructose-1-phosphate and eventually to damage mainly to liver and kidney. Among the sugars, glucose, which reflects blood glucose levels, is metabolized through a different pathway, and HFI patients have no problems with glucose ingestion. In recent years, the effect of fructose has been studied for use as a parenteral nutritional agent and sweetener for diabetic patients; however, administration of these fructose-containing nutritional supplements and foods to individuals unaware of their HFI may cause serious symptoms, and caution is therefore required.

2. Epidemiology

In Europe and the US, more than 100 HFI patients representing several tens of families have been reported. In Europe, the incidence rate of HFI is estimated to be around 1/20 000 to 1/30 000 live births. There have been only a few reports in Japan. It can thus be seen that HFI is a very rare disease. HFI is deeply related to dietary habits; it develops after puberty in some cases; and it seems that there are many patients whose HFI remains unnoticed.

3. Classification

HFI is classified as acute or chronic; acute HFI of infancy occurs in infancy and chronic HFI develops in older children and adults. The symptoms of acute HFI of infancy are more serious the younger the infants are when they develop the disease. No abnormalities are found at birth and the onset is delayed in breast-fed infants. Once solid foods are introduced in infancy, almost all the patients have poor feeding, vomiting, and poor weight gain. Symptoms rapidly progress to hypoglycaemic attack, apnoeic attack, loss of consciousness, and convulsions. Bleeding tendency may manifest as an initial symptom in some patients. Hepatomegaly, ill complexion, and abdominal distension are seen in 50% or more of the patients. Due to the rapid progression of hepatic failure, the patients suffer from anaemia, ascites, anasarca, and bleeding, and ultimately go into shock. If fructose-containing food is not eliminated, it is highly probable that the patients will have a fatal outcome within a month.

Chronic HFI develops mainly from the age of 1 onwards. Common symptoms are hepatomegaly, renal disorder, and liver disorder, as well as developmental disturbance, and nausea/vomiting and hypoglycaemia following fructose ingestion. Long-term intake of fructose causes hepatic cirrhosis, renal acidaemia, and vitamin D-resistant rickets. As disease-specific findings, the patients develop a dramatic aversion to a sweet taste and instinctively refrain from eating fructose-containing sweets. As a consequence, the incidence of dental caries is low among HFI patients.

4. Etiology

HFI is caused by genetic deficiency of the enzyme aldolase B (ALD-B). Deficiency of this enzyme impairs fructose metabolism through the metabolic pathway of fructose-1-phosphate, leading to abnormal accumulation of fructose-1-phosphate.

HFI is inherited as an autosomal recessive trait, and the ALDOB gene encoding the ALD-B enzyme is located on chromosome 9q22.3. More than 30 genetic abnormalities have been reported in HFI patients to date; and the most prevalent 3 mutations are Ala149Pro, Ala174Asp, and Asn334Lys, of which, it is believed, Ala149Pro accounts for the majority of the mutations. Besides missense mutations, nonsense mutations, deletions, and splicing abnormalities have also been reported; however, there are no genotype-phenotype correlations identified for HFI.

5. Pathology

Blocking of metabolism of fructose-1-phosphate causes trapping of inorganic phosphate, leading to marked reductions in serum inorganic phosphate levels and intracellular adenosine triphosphate (ATP; a source of energy in living organisms). Pathological conditions are classified as direct effects of the accumulation of fructose-1-phosphate and secondary metabolic disturbances.

Depletion of ATP in the liver, renal tubules, and small intestinal villus epithelium, where ALD-B is

present, provokes tissue and other dysfunctions, which lead to necrosis. Common findings are impaired liver cells, leakage of liver enzymes, jaundice, and hypoproteinaemia and hypocoagulability resulting from reduced capacity of protein synthesis. Symptoms of renal disorder include aminoaciduria, phosphaturia, and acidaemia. Nausea, vomiting, and diarrhea that become manifest within a few minutes after fructose ingestion are considered to be caused by dysfunction of the small intestine.

Hyperuricaemia and hyperlactacidaemia are found as secondary disorders. Acidaemia also develops due to renal disorder, and the internal environment further becomes more acidic. Hypoglycaemia is then caused in an environment where sugars are no longer produced, and sugars stored in the liver are not released.

6. Diagnosis and Differential Diagnosis

An intravenous load of fructose (intravenous administration of 200 mg/kg for 5 minutes) is given to make the diagnosis while carefully monitoring potential hypoglycaemia. Within 20 minutes of the fructose load, symptoms of acute poisoning as well as fructosuria, hyperfructosaemia, hypophosphataemia, hyperbilirubinaemia, and elevated liver enzymes are observed. A diagnosis of chronic HFI is often made by the fructose tolerance test. It is difficult to confirm the diagnosis if hepatic disorder has already progressed. Infants presenting with hypoglycaemia or decreased blood phosphate levels have sufficient reason to be suspected of having acute HFI of infancy, and it is dangerous to perform tolerance testing of these infants because it induces symptoms.

A definitive diagnosis of HFI requires assessment of histological features and measurement of enzymatic activity by liver biopsies. DNA-based diagnosis is available by searching for highly frequent gene mutations, and DNA analysis is also performed for carrier screening.

In infants, all diseases associated with hepatomegaly, jaundice, and repetitive vomiting should be included in the differential diagnosis of HFI. Among congenital metabolic disorders, galactosaemia and tyrosinaemia are very similar to HFI. High blood galactose levels and cataract for the former, and high α-fetoprotein levels for the latter are useful for the differential diagnosis.

7. Treatment and Prognosis

The treatment of HFI is the complete elimination of fructose from the diet. In infancy, the patients should not ingest any fructose-containing foods such as fruit juice, sucrose, or honey. After weaning from breast milk, caution is required about avocado, and chocolate because these foods contain large amounts of fructose. Since HFI is often diagnosed in adulthood, it is clear that the prognosis of HFI after infancy is favorable. However, caution is required because HFI may be identified in some asymptomatic patients only after they experience serious symptoms after receiving fructose or sorbitol-containing fluid administration. There have also been reports of cases of heterozygous carriers of ALDOB mutations who developed hypoglycaemia, hepatic impairment, and other symptoms after receiving an excessive fructose load.

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated March 1 and 19, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Baloxavir marboxil

Branded name (name of company)	Xofluza Tablets 10 mg, 20 mg, Xofluza granule 2% portions (Shionogi & Co., Ltd.)
Therapeutic category	Antivirals
Indications	Influenza A and B viral infections

PRECAUTIONS (revised language is underlined)

Important precautions	Bleeding may occur. Patients and their families should be informed that: 1) The attending physician should be contacted if bloody stool, epistaxis, haematuria, or other forms of bleeding are observed. 2) These symptoms may appear several days after administration of this drug.
Interactions (Precautions for Co-administration)	Warfarin
Adverse reactions (clinically significant adverse reactions)	**Bleeding:** Bloody stool, epitaxis, haematuria, or other forms of bleeding may occur. Appropriate measures should be taken if these symptoms appear.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 47-month period (April 2015 to February 2019). Cases involving bleeding: 13 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 7 800 000 Japanese market launch: March 2018

Case summary

Case 1 (melena)

<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
20s</td><td>Influenza
(none)</td><td>40 mg
Once</td><td>Melaena
Medical history: none
1 day before administration: The patient had pyrexia.
Day 1 of administration (day of termination): Influenza test was positive (+). Baloxavir marboxil 40 mg/day was orally administered for influenza.
1 day after termination: Diarrhoea occurred every 30 minutes from the night. After a while, blood began to be seen in the stool (diarrhoea and melaena developed).
2 days after termination: The patient visited this hospital, and bloody stool was confirmed. Stool testing showed O antigens (-), shigella (-), salmonella (-), vibrio (-), campylobacter (-). Tenderness was found in the left abdominal area by palpation.
6 days after termination: Recovery was confirmed (diarrhoea and melaena resolved).
Laboratory Examination
<table>
<tr><th></th><th>Day of administration (at delivery)</th><th>2 days after termination</th></tr>
<tr><td>Red blood cell count (RBC) x 10E4/uL</td><td>444</td><td>458</td></tr>
<tr><td>Hemoglobin (Hb) g/dL</td><td>13</td><td>13.4</td></tr>
<tr><td>White blood cell count (WBC) /uL</td><td>6 000</td><td>6 200</td></tr>
<tr><td>Differential leucocyte count: neutrophils (NEU) %</td><td>51</td><td>55</td></tr>
<tr><td>Differential leucocyte count: lymphocytes (LYM) %</td><td>7</td><td>6</td></tr>
<tr><td>Platelet count x 10E4/uL</td><td>19.8</td><td>16.7</td></tr>
<tr><td>CRP mg/dL</td><td>6.3</td><td>4.6</td></tr>
</table>
</td></tr>
<tr><td colspan="5">Concomitant medications: Maobushisaishinto, acetaminophen</td></tr>
</table>

Case 2 (increased international normalized ratio)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Influenza A (none)	40 mg Once	**Increased international normalized ratio** Medical history: aortic incompetence, mitral valve incompetence, double valve replacement 1 day before administration: Pyrexia, headache, and low-back pain (+) Day 1 of administration (day of termination): Influenza A positive. Baloxavir marboxil 40 mg/day was administered for influenza A. 6 days after termination: Regular outpatient visit. Blood testing was performed. 7 days after termination: In the test results, PT-INR was undetectable and the PT time was ≥60.0. Discontinuation of warfarin potassium was instructed (PT-INR prolongation developed). 8 days after termination: Re-examination was performed. Bruise developed. 11 days after termination: PT-INR was 5.43 8 days after termination. As pneumonia was suspected on the X-ray image, clavulanate potassium/amoxicillin hydrate was prescribed. 13 days after termination: Examination. INR and CRP were 4.07 and 6.56 11 days after termination, respectively. Warfarin potassium had been orally administered at a reduced dose. 14 days after termination: INR was 4.10 13 days after termination. The dose of warfarin was reduced. 17 days after termination: Blood testing was performed. 18 days after termination: Because of INR 2.30, the dose of warfarin potassium was returned to the previously prescribed one. 32 days after termination: Blood testing showed PT-INR 2.66.

Laboratory Examination

	Days after termination of administration					
	6 days	8 days	11 days	13 days	17 days	32 days
PT time (SEC)	≥60.0	59.4	44.9	45.3	-	-
Control (SEC)	11.5	11.5	11.5	11.5	-	-
PT activity value	<10.0	<10.0	12.8	12.6	-	-
PT-INR	Undetectable	5.43	4.07	4.10	2.30	2.66

Suspected concomitant medications: warfarin potassium
Concomitant medications: azosemide, carvedilol, verapamil hydrochloride, vonoprazan fumarate

Case 3 (mouth haemorrhage)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 70s	Influenza (chronic myeloid leukemia, reflux esophagitis, hypertension)	40 mg Once	**Mouth hemorrhage** Medical history: cholelithiasis 3 days before administration: The patient visited the hospital, complaining of cough, sputum, pharyngodynia, and nasal discharge that were present from the preceding day. As the symptoms were regarded as acute upper respiratory tract inflammation and acute bronchitis, salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate combination tablets, dimemorfan phosphate, ambroxol hydrochloride, and clarithromycin were prescribed for 3 days. Day 1 of administration (day of termination): The patient complained of pyrexia (38.8°C), cough, and sputum that were present from 2 days before. Using a rapid kit, the patient was diagnosed with influenza (A). Baloxavir marboxi 40 mg/day was orally administered. Due to mouth haemorrhage that started approximately 3 hours later, the patient visited the hospital. As haemorrhage was seen throughout the oral mucosa, carbazochrome sodium sulfonate and tranexamic acid were administered as hemostatic agents for 1 day. 1 day after termination: Mouth haemorrhage improved (remitted) at the time of the visit.

Laboratory Examination

	1 day after termination
Red blood cell count (× 10^4/mm^3)	400
Hemoglobin (g/dL)	11.9
White blood cell count (/mm^3)	7 430
: Neutrophils (%)	47.2
: Eosinophils (%)	0.5
: Lymphocytes (%)	43.3
Platelet count (× 10^4/mm^3)	22.0
AST (GOT) (IU/L)	35
ALT (GPT) (IU/L)	16
ALP (IU/L)	215
LDH (IU/L)	245
Total bilirubin (mg/dL)	0.4

		Total protein (g/dL)	7.4	
		BUN (mg/dL)	23.5	
		Serum creatinine (mg/dL)	1.45	
		Serum Na (mEq/L)	137	
		Serum K (mEq/L)	4.6	
		Serum Cl (mEq/L)	100	
	Concomitant medications: dasatinib, losartan potassium, ecabet sodium, salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate combination tablets, dimemorfan phosphate, ambroxol hydrochloride, clarithromycin, indometacin			

2 Quetiapine fumarate

Branded name (name of company)	a. Seroquel 25 mg Tablets, 100 mg Tablets, 200 mg Tablets, Seroquel Fine Granules 50% (Astellas Pharma Inc.), and the others b. Bipresso Extended Release Tablets 50 mg, 150 mg (Astellas Pharma Inc.)
Therapeutic category	Psychotropics
Indications	a. Schizophrenia b. Improvement of depressive symptoms in patients with bipolar disorder

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme:** Toxic epidermal necrolysis, oculomucocutaneous syndrome, or erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 45-month period (April 2015 to December 2018). Cases involving toxic epidermal necrolysis: a, b; 1 (no patient mortalities), oculomucocutaneous syndrome: a, b; 0, erythema multiforme: a, b; 0 Number of patients using the drug as estimated by the MAH during the previous 1-year period: a: approximately 210 000, b: approximately 26 000 Japanese market launch: a; February 2001, b; October 2017

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures	
	Female 40s	Insomnia (anti-NMDA receptor encephalitis) (symptomatic epilepsy)	12.5mg (for 4 days) 50mg (for 3 days)	**Toxic epidermal necrolysis** Height: 155 cm, Weight: 48.6 kg Past history of adverse reactions: none Alcohol drinking: unknown Smoking: none Allergy: none	
				7 days before administration	Administration of levetiracetam dry syrup 3 000 mg/day was initiated for anti-NMDA receptor encephalitis and symptomatic epilepsy.
				Day 1 of administration:	Quetiapine fumarate 12.5 mg/day was initiated for insomnia. Lacosamide tablets 100 mg/day were initiated for symptomatic epilepsy.
				Day 5 of administration:	The dose of quetiapine fumarate was increased to 25 mg/day.
				Day 7 of administration: (day of onset)	Papules appeared on the face, precordial region, and upper extremities, accompanied by pruritus. Topical use of diphenhydramine cream was initiated.
				Day 8 of administration: (day of discontinuation)	The dose of lacosamide was increased to 200 mg/day. Betamethasone/d-chlorpheniramine maleate combination tablets were initiated. Administration of quetiapine fumarate was discontinued.
				1 day after discontinuation:	Pyrexia of 39°C. Blisters appeared on the left lower jaw. Skin biopsy was performed. The results showed necrotic keratinocytes and liquefaction degeneration of the basal layer, but showed neither intra-epidermal blisters, multinucleated giant cells, nor acantholytic cells, and therefore the event was suspected to be drug-induced. Lacosamide was discontinued.
				2 days after discontinuation:	Oral administration of prednisolone 50 mg/day was initiated. Topical use of sulfadiazine ointment and white petrolatum was initiated.
				5 days after discontinuation:	Epidermolysis area: >30%. Administration of IVIG 20 g/day for 5 days (high-dose intravenous immunoglobulin) and cefazolin sodium injection was initiated. Levetiracetam was discontinued.
				6 days after discontinuation:	Methylprednisolone sodium succinate 1 g for injection for 3 days (steroid pulse), betamethasone sodium phosphate ophthalmic solution, and moxifloxacin hydrochloride ophthalmic solution were initiated.
				8 days after discontinuation:	Epidermolysis area: 90%. Bepotastine besilate tablets were initiated for pruritus.
				12 days after discontinuation:	Administration of IVIG 20 g/day for 5

					days was initiated. 15 days after discontinuation: Tapering of prednisolone was initiated. 28 days after discontinuation: Toxic epidermal necrolysis remitted. 40 days after discontinuation: Prednisolone was discontinued. Date unknown: Drug-induced lymphocyte stimulation test (DLST) was performed. The results of DLST showed quetiapine positive (SI 2.2), lacosamide negative (SI 1.4), and levetiracetam negative (SI 1.1).

Laboratory Examination

	8 days before administration	1 day after termination	8 days after termination	28 days after termination
WBC (cells/μL)	10 759	9 500	5 460	6 950
CRP (mg/dL)	1.26	0.47	3.74	0.23
Body temperature (Cel)		39		

Suspected concomitant medications: lacosamide, levetiracetam
Concomitant medications: antibiotics-resistant lactic acid bacteria preparation, *Lactobacillus casei* preparation, *Clostridium butyricum* preparation, ramelteon, suvorexant, brotizolam, mosapride citrate hydrate, pantethine, esomeprazole magnesium hydrate, edoxaban tosilate hydrate, potassium gluconate, aciclovir, dexmedetomidine hydrochloride, propofol, haloperidol, acetaminophen, midazolam

3 (1) Vonoprazan fumarate
(2) Vonoprazan fumarate/amoxicillin hydrate/clarithromycin
(3) Vonoprazan fumarate/amoxicillin hydrate/metronidazole

Branded name (name of company)	(1) Takecab Tablets 10 mg., 20 mg. (Takeda Pharmaceutical Company Limited.) (2) Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited.) (3) Vonopion Pack (Takeda Pharmaceutical Company Limited.)
Therapeutic category	Peptic ulcer agents, Antibiotics-Miscellaneous
Indications	(1) Treatment of gastric ulcer, duodenal ulcer, reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration Adjunct therapy to *Helicobacter pylori* eradication in the following: Gastric or duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early-stage gastric cancer, or *Helicobacter pylori* gastritis (2) <Applicable microorganisms> Strains of *Helicobacter pylori* susceptible to amoxicillin and clarithromycin <Applicable conditions> *Helicobacter pylori* infection in the stomach and *Helicobacter pylori* gastritis after endoscopic treatment of gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, or early-stage gastric cancer (3) <Applicable microorganisms> Strains of *Helicobacter pylori* susceptible to amoxicillin and metronidazole <Applicable conditions> *Helicobacter pylori* infection in the stomach and *Helicobacter pylori* gastritis after endoscopic treatment of gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, or early-stage gastric cancer

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**<u>Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme:</u>** <u>Toxic epidermal necrolysis, oculomucocutaneous syndrome, or erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.</u>
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 45-month period (April 2015 to December 2018). Cases involving; toxic epidermal necrolysis: (1) 1 (no patient mortalities), (2) 1* (no patient mortalities), (3) 0

oculomucocutaneous syndrome: (1) 2 (no patient mortalities), (2) 14* (no patient mortalities), (3) 0
erythema multiforme: (1) 1 (no patient mortalities), (2) 50* (no patient mortalities), (3) 3* (no patient mortalities)
* Causalities not assessed.

Number of patients using the drug as estimated by the MAH during the previous 1-year period: (1): approximately 9 800 000

Japanese market launch: (1): February 2015, (2): June 2016, (3): June 2016

Case summary

< Summary of a case of toxic epidermal necrolysis treated with Takecab Tablets>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Product use for unknown indication (muscle abscess, spondylitis)	20 mg For 86 days ↓ Discontinued	Toxic epidermal necrolysis Medical history: hypertension, dyslipidaemia, benign prostatic hyperplasia, atrial fibrillation, spinal fusion surgery Day 1 of administration: At Hospital A, this drug was prescribed and administration was initiated (20 mg/day). Approximately 2 months after administration: Having been diagnosed with iliopsoas abscess and purulent spondylitis, the patient was admitted to Hospital B. Day 56 of administration: Intravenous drip infusion of meropenem hydrate (1.0 g/day) was initiated. Day 65 of administration: Posterior spine fusion was performed. Day 84 of administration: As skin eruption appeared, the patient visited the dermatology department of the same hospital. Enanthema was not clearly identified, and erythema developed at multiple sites on the whole body with a tendency toward fusion. Day 86 of administration (day of discontinuation): With the oral intake on this day, this drug was discontinued. As drug eruption was suspected, medical treatment was initiated with a switch of antimicrobial drug (cefmetazole sodium drip infusion [2.0 g/day]) and topical steroids. 1 day after discontinuation: Pyrexia of 38.4°C and erythema/erosion on the face and body trunk/extremities were observed. 3 days after discontinuation: Erosion associated with a tendency toward bleeding was seen on the lips and a tendency toward spread of skin eruption persisted, and consequently, for suspected toxic epidermal necrolysis (TEN), the patient was referred to Hospital C and urgently admitted to the hospital. At the time of hospital admission, extended erosion was observed in the mouth and on the lips and genital area, but without eye mucosal eruption. Dark reddish to brownish oval erythema was fused on the body trunk including the face and the extremities. It was seen diffusely in some areas. Erosion and blisters were observed on the precordial region/upper back and thighs. The epidermolysis area accounted for 30% and the SJS/TEN severity score was 8 points, showing a severe state. On the day of hospital admission, systemic administration of

				8 days after discontinuation 11 days after discontinuation 27 days after discontinuation 38 days after discontinuation	steroids at 2 mg/kg/day in prednisolone equivalence was initiated. Because TEN occurred during medical treatment of iliopsoas abscess, concomitant high-dose intravenous immunoglobulin (IVIg therapy at 500 mg/kg/day for 5 days) was initiated simultaneously with systemic steroid therapy. In addition, local therapy to cover the sites of erosion/blisters with gauze after topical use of Baramycin (bacitracin) ointment was performed. After that, new formation of erosion stopped and epithelialization was favorable, and therefore the dose of prednisolone was tapered after confirming the absence of corneal disorder. Marked epithelialization was observed. As almost all of the erosion surfaces became epithelialized, administration of prednisolone was terminated. The patient was transferred to Hospital B for the purpose of rehabilitation.
	<Results of DLST> This drug; positive: meropenem hydrate; negative (SI value: this drug 2.2, meropenem hydrate 1.6; positive with SI value ≥1.8). <Results of histopathology examination> Cell necrosis was seen at many sites in all layers of the epidermis. Formation of clefts was observed beneath the epidermis and re-epithelialization was observed partially in the basal layer. In the superficial dermis, infiltration of inflammatory cells, mainly mononuclear cells, was observed in perivascular tissue. <Differential diagnosis> • Staphylococcal scalded skin syndrome: It was ruled out because bacterial culture was all negative for the local skin regions, pharynx, and blood and the histopathology findings were different. • Toxic shock syndrome: It was ruled out because there were no shock symptoms during the clinical course and the histopathology findings were different. • Acute generalized exanthematous pustulosis: It was ruled out because of absence of pustules as a rash characteristic and the histopathology findings. • Autoimmune bullosa: It was ruled out because of lack of autoantibodies and the histopathology findings. <Established diagnosis> During the clinical course, blisters and erosion based on necrotizing lesions of the epidermis were observed on 30% of the body surface area in association with pyrexia in the range of 38°C and generalized erythema, and the above diseases to be differentiated could be ruled out, thereby meeting the four main items in the diagnostic criteria for TEN 2016 in Japan. In addition, erythema accompanied by flat atypical targets was seen, signs of severe symptoms and eating disorder were present as systemic symptoms, and full thickness necrosis of the epidermis was revealed by histopathology, and therefore the patient was diagnosed with TEN. Relatively mild hyperemia was the only ocular symptom.				
	Suspected concomitant medications: meropenem hydrate Concomitant drugs: none				

< Summary of a case of oculomucocutaneous syndrome treated with Takecab Tablets>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Gastroesophageal reflux disease (diabetes mellitus, dyslipidaemia, hypertension)	20 mg For 16 days ↓ Discontinued	Stevens-Johnson syndrome Medical history: none Approximately 1 year and 7 months before administration: Oral administration of imidapril hydrochloride, amlodipine besilate, pravastatin sodium, sitagliptin phosphate hydrate, and voglibose was initiated. 7 days before administration: The patient was orally receiving rabeprazole sodium for reflux esophagitis, but due to gastroesophageal reflux disease (grade C), rabeprazole sodium was discontinued. Administration of mosapride citrate hydrate and sodium alginate was initiated. Day 1 of administration: Administration of this drug was initiated. Day 14 of administration: Pyrexia, pharyngodynia, and erythema on the whole body were observed. Day 15 of administration: It was accompanied by oral pain and erosion. Day 16 of administration (day of discontinuation): The patient visited Hospital A. With the oral intake on this day, the oral drugs including this drug were all discontinued (because of erythema iris on the whole body and oral/lip ulcers accompanied by pyrexia of 38°C, the patient was diagnosed with Stevens-Johnson syndrome). Steroid pulse therapy (methylprednisolone sodium succinate 500 mg/day) was performed (for 3 days). 3 days after discontinuation: After steroid pulse therapy, pyrexia promptly abated. Erythema on the whole body also began to have a tendency toward fading. Ocular complications were noted at a visit to an ophthalmologist. The dosage form of prednisolone (40 mg/day) was changed to oral administration. Thereafter the dose of oral prednisolone was tapered. 18 days after discontinuation: The dose of prednisolone was reduced (15 mg/day), and the patient was discharged from the hospital on the same day. 38 days after discontinuation: Administration of oral prednisolone was terminated. 81 days after discontinuation: The patient recovered.
	<Results of DLST> This drug: negative Sitagliptin phosphate hydrate: negative			

	Amlodipine besilate: negative Imidapril hydrochloride: negative (SI value: this drug 58%, sitagliptin phosphate hydrate 85%, amlodipine besilate 89%, imidapril hydrochloride: 126%). <Results of histopathology examination> Vacuolar degeneration of the dermal-epidermal border region; lymphocytic infiltration of the intra-epidermal region to dermal-epidermal border region.
	Suspected concomitant medications: voglibose, imidapril hydrochloride, amlodipine besilate, pravastatin sodium, sitagliptin phosphate hydrate, mosapride citrate hydrate, sodium alginate Concomitant drugs: none

< Summary of a case of erythema multiforme treated with Takecab Tablets>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Helicobacter infection (food allergy)	40 mg For 7 days	Erythema multiforme Medical history: nephrotic syndrome, drug eruption Day 1 of administration: At Hospital A, administration of this drug, amoxicillin hydrate, clarithromycin, and antibiotics-resistant lactic acid bacteria preparation was initiated for eradication of *Helicobacter pylori*. Day 7 of administration (day of termination): At night, the patient became aware of redness and skin eruption with mild pruritus on the bilateral flanks. With the oral intake on this day, administration of this drug, amoxicillin hydrate, clarithromycin, and antibiotics-resistant lactic acid bacteria preparation was terminated. 1 day after termination: Swelling of the eyes and lips was observed, and pale erythema also appeared on the face. Skin eruption on the body trunk also extended. The patient visited Hospital B, and as drug eruption was suspected, fexofenadine hydrochloride and betamethasone/*d*-chlorpheniramine maleate combination tablets were prescribed. 2 days after termination: Due to worsening of the symptoms, the patient visited the emergency outpatient unit of Hospital C. At the initial visit, pyrexia 37.4°C, blood pressure 150/95 mmHg, pulse rate 126/min, SpO_2 98%; consciousness was lucid. Hyperemia was present in the palpebral conjunctiva and bulbar conjunctiva, without visual field disorders. Lip swelling and small erosion of the upper lip were present, and redness was also observed in the hard palate. On the whole body including the face, rice-grain to hen's egg-sized palpable disseminated erythema was distributed. Erythema developed as target-shaped patches, with a tendency toward confluence. Blisters and erosion were not observed on the skin and genital area. Nikolsky phenomenon was negative. Pruritus was mild. The patient was diagnosed with erythema multiforme exudativum (severe) and admitted to the hospital. Administration of prednisolone (40 mg/day) and clobetasol propionate ointment was initiated. 3 days after termination: Pyrexia abated, improvement of ocular hyperemia, and improvement of swelling of the palpebra/lips were observed. For mild hyperemia of the eyelid mucosa, moxifloxacin hydrochloride ophthalmic solution and fluorometholone ophthalmic solution were prescribed. DLST was performed. 4 days after termination: Erythema on the face tended to disappear. Erythema on the body trunk and extremities left brown pigmentation at the center of patches.

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
				5 days after termination: *d*-chlorpheniramine maleate (2 mg) was used as needed when pruritus occurred. 9 days after termination: The dose of prednisolone was reduced (20 mg/day). Pruritus remitted. Skin eruption on the body trunk and extremities tended to disappear. 12 days after termination: The dose of prednisolone was reduced (10 mg/day). 15 days after termination: Swelling and erosion of the lips only left blisters on the lower right lip, and erythema on the whole body became pigmented. Prednisolone was discontinued. Thereafter, the symptoms improved without relapse. 16 days after termination: The doses of moxifloxacin hydrochloride ophthalmic solution and fluorometholone ophthalmic solution were reduced to twice daily and administration was to be terminated with already dispensed solution finished by the patient. 19 days after termination: After discontinuation of steroids, the clinical course was favorable. The patient recovered and was discharged from the hospital.
	<Results of DLST> This drug: positive, amoxicillin hydrate, clarithromycin: negative (SI value: this drug 183%, amoxicillin hydrate 130%, clarithromycin 163%).			
	Suspected concomitant medications: amoxicillin hydrate, clarithromycin Concomitant medications: antibiotics-resistant lactic acid bacteria preparation			

4

Revision of Precautions (No. 302)

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 March 1, and 19, 2019.

1 Antivirals
Oseltamivir phosphate

Branded name	Tamiflu capsules 75, Tamiflu dry syrup 3% (Chugai Pharmaceutical Co., Ltd.), and the others
Important precautions	Bleeding may occur. Patients and their families should be informed to contact the attending physician if any haemorrhage symptom such as bloody stool, haematemesis, or metrorrhagia are observed.
Interactions (Precautions for Co-administration)	Warfarin

2 Antivirals
Baloxavir marboxil

Branded name	Xofluza Tablets 10 mg, 20 mg, Xofluza granule 2% portions (Shionogi & Co. Ltd.)
Important precautions	Bleeding may occur. Patients and their families should be informed that: 1) The attending physician should be contacted if bloody stool, epistaxis, haematuria, or other forms of bleeding are observed. 2) These symptoms may appear several days after administration of this drug.
Interactions (Precautions for Co-administration)	Warfarin
Adverse reactions (clinically significant adverse reactions)	**Bleeding:** Bloody stool, epitaxis, haematouria, or other forms of bleeding may occur. Appropriate measures should be taken if these symptoms appear.

3 **Psychotropics**

Quetiapine fumarate

Branded name

a. Seroquel 25 mg Tablets, 100 mg Tablets, 200 mg Tablets, Seroquel Fine Granules 50% (Astellas Pharma Inc.), and the others
b. Bipresso Extended Release Tablets 50 mg, 150 mg (Astellas Pharma Inc.)

Adverse reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme:
Toxic epidermal necrolysis, oculomucocutaneous syndrome, or erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken

4 **Psychotropics**

Clozapine

Branded name

Clozaril Tablets 25 mg, 100 mg (Novartis Pharma K.K.)

Adverse reactions (clinically significant adverse reactions)

Intestinal obstruction, paralytic ileus, intestinal ulcer, intestinal perforation:
Cases of intestinal obstruction, paralytic ileus, intestinal ulcer, or intestinal perforation that occurred by the anticholinergic effect of this drug and resulted in mortality have been reported. If any abnormalities such as constipation are observed, appropriate measures should be taken.

5 **Peptic ulcer agents, Antibiotics-Miscellaneous**

[1] Vonoprazan fumarate
[2] Vonoprazan fumarate/amoxicillin hydrate/clarithromycin
[3] Vonoprazan fumarate/amoxicillin hydrate/metronidazole

Branded name

[1] Takecab Tablets 10 mg., 20 mg. (Takeda Pharmaceutical Company Limited.)
[2] Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited.)
[3] Vonopion Pack (Takeda Pharmaceutical Company Limited.)

Adverse reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme:
Toxic epidermal necrolysis, oculomucocutaneous syndrome, or erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

6 Miscellaneous metabolism agents-Miscellaneous

Denosumab (genetical recombination) (120 mg product)

Branded name	Ranmark Subcutaneous Injection 120 mg (Daiichi Sankyo Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Hypercalcaemia after discontinuation of denosumab treatment:** In patients with bone giant cell tumour, hypercalcaemia may occur after discontinuation of denosumab treatment. **Multiple vertebral fractures after discontinuation of denosumab treatment:** Multiple vertebral fractures may occur after discontinuation of denosumab treatment.

7 Preparations containing sorbitol as excipient (intravenous injections)

Branded name	-
Careful Administration	Patients with hereditary fructose intolerance (fructose, a metabolite produced in the body from D-sorbitol** added to the product as excipient cannot be broken down, which may induce hypoglycemia, hepatic failure, renal failure, etc.) ** “D-sorbitol” here should be replaced with "sorbitol" for products with their current package inserts specifying "sorbitol."

8 Preparations containing fructose as excipient (intravenous injections)

Branded name	-
Careful Administration	Patients with hereditary fructose intolerance (fructose added to the product as excipient cannot be broken down, which may induce hypoglycemia, hepatic failure, renal failure, etc.)

5

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 ADR 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 February 28, 2019)
◎: Products for which EPPV was initiated after February 1, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Binimetinib Mektovi Tablets 15 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
◎	Encorafenib Braftovi Capsules 50 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
◎	Sofosbuvir/velpatasvir Epclusa Combination Tablets	Gilead Sciences Inc.	February 26, 2019
◎	Metirosine Demser Capsules 250 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
◎	Damoctocog alfa pegol (genetical recombination) Jivi for i.v. injection 250, 500, 1000, 2000, 3000	Bayer Yakuhin Ltd	February 12, 2019
	Secukinumab (genetical recombination) *1 Cosentyx for s.c. injection 150 mg syringe	Novartis Pharma K.K.	December 21, 2018
	Ipragliflozin L–proline *2 Suglat Tablets 25 mg, 50 mg	Astellas Pharma Inc.	December 21 2018
	Dolutegravir sodium/rilpivirine hydrochloride Juluca Combination Tablets	Viiv Healthcare K.K.	December 20, 2018
	Gilteritinib fumarate Xospata Tablets 40 mg	Astellas Pharma Inc.	December 3, 2018
	Abemaciclib Verzenio Tablets 50 mg, 100 mg, 150 mg	Eli Lilly Japan K.K.	November 30, 2018
	Dexmedetomidine hydrochloride a. Precedex Intravenous Solution 200 μg [Pfizer], b. Precedex Intravenous Solution 200 μg/50 mL syringe [Pfizer], c. Precedex Intravenous Solution 200 μg [Maruishi], d. Precedex Intravenous Solution 200 μg/50 mL syringe [Maruishi]	a, b Pfizer Japan Inc. c, d Maruishi Pharmaceutical Co., Ltd.	November 29, 2018
	Macrogol 4000/sodium chloride/sodium bicarbonate/potassium chloride Movicol Combination Powder	EA Pharma Co., Ltd.	November 29, 2018
	Omidenepag isopropyl Eybelis Ophthalmic Solution 0.002%	Santen Pharmaceutical Co., Ltd.	November 27, 2018

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Vibegron Beova Tablets 50 mg	Kyorin Pharmaceutical Co.,Ltd.	November 27, 2018
Blinatumomab (genetical recombination) Blincyto I.V. Infusion 35 μg	Amgen Astellas Bi-Pharma K.K.	November 27, 2018
Lorlatinib Lorbrena Tablets 25 mg, 100 mg	Pfizer Japan Inc.	November 20, 2018
Icatibant acetate Firazyr subcutaneous injection 30 mg syringe	Shire Japan KK	November 20, 2018
Vedolizumab (genetical recombination) Entyvio for I.V. Infusion 300 mg	Takeda Pharmaceutical Company Limited.	November 7, 2018
Nonacog beta pegol (genetical recombination) Refixia I.V. Injection 500, 1000, 2000	Novo Nordisk Pharma Ltd.	November 1, 2018
Levonorgestrel/ethinylestradiol Jemina Tablets	Nobelpharma Co., Ltd.	October 4, 2018
Spiramycin Spiramycin 1.5M IU Tablets [Sanofi]	Sanofi K.K.	September 25, 2018
Rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate Odefsey Combination Tablets	Janssen Pharmaceutical K.K.	September 20, 2018
Fidaxomicin Dafclir Tablets 200 mg	Astellas Pharma Inc.	September 18, 2018

*1 Ankylosing spondylitis that does not adequately respond to existing treatments

*2 Type 1 diabetes mellitus