Pharmaceuticals and Medical Devices Safety Information

No. 336 September 2016

Table of Contents

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Pharmaceuticals and Medical Devices Safety Information

No. 336 September 2016

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

A-aDO_2	Alveolar-arterial difference in oxygen tension
ADR	Adverse drug reaction
Alb	Albumin
ALP	Alkaline phosphatase
ALT/GPT	Alanine aminotransferase (Glutamate pyruvate transaminase)
ANA	Antinuclear antibody
AST/GOT	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computed tomography
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
DNA	Deoxyribonucleic acid
DRESS/DIHS	Drug reaction with eosinophilia and systemic symptoms / Drug-induced hypersensitivity syndrome
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
Eos	Eosinophil
EPPV	Early post-marketing phase vigilance
Ex19del	Exon 19 deletion
FA	Fluorescent antibody
γ-GTP	Gamma-glutamyl transpeptidase
HBV	Hepatitis B virus
HHV-6	Human herpes virus 6
HLA	Human leukocyte antigen
Ig	Immunoglobulin
ILD	Interstitial lung disease
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
NIHS	National Institute of Health Sciences
PaO_2	Arterial oxygen pressure
PMDA	Pharmaceuticals and Medical Devices Agency
PS	Performance status
S.I.	Stimulation index
SJS	Stevens-Johnson syndrome
SpO_2	Arterial oxygen saturation
TEN	Toxic epidermal necrolysis
VCA	Viral capsid antigen
WBC	White blood cell

1

Precautions Relating to Interstitial Lung Disease During Administration of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Non-proprietary name	a. Gefitinib, b. Erlotinib hydrochloride, c. Afatinib maleate, d. Osimertinib mesilate, e. Nivolumab (genetical recombination)
Brand name (name of company)	a. IRESSA Tablets 250 (AstraZeneca) b. TARCEVA Tablet 25mg, 100mg, 150mg (Chugai Pharmaceutical) c. Giotrif Tablets 20mg, 30mg, 40mg, 50mg (Nippon Boehringer Ingelheim) d. Tagrisso Tablets 40mg and 80mg (Astrazeneca) e. Opdivo Intravenous Infusions 20 mg and 100 mg (Ono Pharmaceutical Co., Ltd.)
Therapeutic category	Antineoplastics-Miscellaneous
Indication	a. EGFR mutation-positive unresectable or relapsed nonsmall-cell lung cancer b. Unresectable, advanced nonsmall-cell lung cancer having aggravated following cancer chemotherapy; EGFR mutation-positive unresectable, relapsed and advanced nonsmall-cell lung cancer with no history of cancer chemotherapy; incurable, unresectable pancreatic carcer (TARCEVA 25mg, 100mg only) c. EGFR mutation-positive unresectable or relapsed nonsmall-cell lung cancer d. EGFR tyrosine kinase inhibitor-resistant, EGFR T790M mutation-positive, unresectable, advanced or relapsed, non-small cell lung cancer e. 1. Radically unresectable malignant melanoma 2. Unresectable, advanced or relapsed non-small cell lung cancer

1. Introduction

The epidermal growth factor receptor tyrosine kinase inhibitors (hereinafter referred to as “EGFR-TKIs”) gefitinib, erlotinib hydrochloride, afatinib maleate, and osimertinib mesilate have been approved for non-small cell lung cancer, and have alerts on their respective package inserts, for example in the Warnings section, relating to potentially life-threatening interstitial lung disease (ILD).

A nivolumab (genetical recombination) formulation (hereinafter referred to as “nivolumab”) was also approved in July 2014 for malignant melanoma, and an alert about ILD has been provided on the package insert, in sections including the Warnings section. However, since the use of nivolumab was approved for non-small cell lung cancer in December 2015, several cases of serious ILD associated with administration of EGFR-TKIs have been reported in patients with non-small cell lung cancer who had a history of treatment with nivolumab. Recently, the Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) confirmed the details of these cases and have disseminated reminders of the precautions when administering EGFR-TKIs to relevant academic societies and similar groups on July 22, 2016 (see Reference 1)). This information has been summarized in this section.

2. Occurrences of interstitial lung disease

As of July 1, 2016, there have been reports of 8 cases with a history of treatment with nivolumab where serious ILD has occurred after administration of EGFR-TKIs for non-small cell lung cancer. Three cases had fatal outcomes (see Table 1). These cases included patients with poor general condition due to progression of the underlying disease, patients with a history of ILD or findings suggesting the disease before administration of EGFR-TKIs, and patients who possibly developed the disease after the termination of nivolumab, judging from the mechanism of nivolumab, etc.

MHLW and PMDA have investigated these cases. At present however, it is unclear whether the extended use of EGFR-TKIs after administration of nivolumab increases the risk of ILD.

3. Precautions when administering EGFR-TKIs

A review of the adverse drug reaction (ADR) reports relating to ILD collected this time revealed cases with a history of ILD or findings suggesting the disease before administration of EGFR-TKIs, sometimes with serious outcomes. The package inserts of EGFR-TKIs contain precautions relating to ILD (see Table 2), stating that EGFR-TKIs should be administered with caution to patients with concurrent or historical ILD, as ILD may be aggravated with a potentially fatal outcome. The MHLW calls for proper use of EGFR-TKIs, by being fully aware of these precautions when administering EGFR-TKIs, checking for concurrent or historical ILD before administration, and monitoring the patient carefully during administration.

To ensure the proper use of nivolumab and osimertinib mesilate, please also refer to the materials for healthcare professionals prepared by the marketing authorization holders (MAHs), and the information provided by the Japanese Society of Medical Oncology to its members (Reference 2) to 4)).

Table 1 Line list of cases where ILD occurred after administration of EGFR-TKIs following nivolumab (as of July 1, 2016)

	Administered EGFR-TKI	Outcome	Outline of identified medical history	History of ILD
1	Gefitinib	fatal	radiotherapy coadministered cisplatin/vinorelbine docetaxel coadministered carboplatin/gemcitabine nivolumab	suspected
2	erlotinib hydrochloride	recovering	radiotherapy nivolumab	Present
3	osimertinib mesilate	fatal	Gefitinib coadministered carboplatin/gemcitabine coadministered carboplatin/paclitaxel docetaxel tegafur-gimeracil-oteracil combination drug afatinib pemetrexed gefitinib nivolumab	Present
4	osimertinib mesilate	recovered	nivolumab	unknown
5	osimertinib mesilate	fatal	Gefitinib pemetrexed	suspected

			nivolumab	
6	osimertinib mesilate	recovering	coadministered erlotinib/bevacizumab coadministered carboplatin/pemetrexed afatinib nivolumab	absent
7	osimertinib mesilate	recovering	Nivolumab	absent
8	osimertinib mesilate	not recovered	Nivolumab	absent

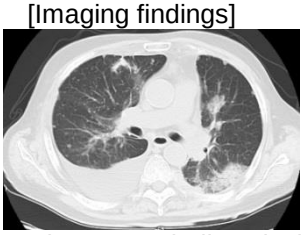
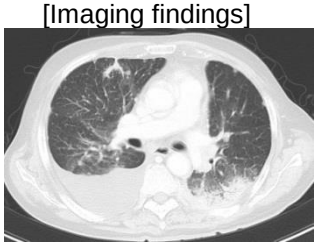
Table 2 Precautions about ILD on the package inserts of EGFR-TKIs

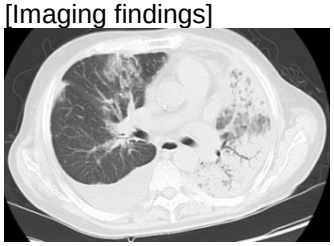
○ Before starting administration of EGFR-TKIs, computed tomography (CT) of the chest and an interview should be performed to check for concurrent or historical ILD, and a careful judgment should be made about whether administration can be started. ○ During the administration period of EGFR-TKIs, the patient should be monitored carefully, for example by checking for the initial symptoms of ILD (such as dyspnoea, cough, and pyrexia) and performing regular chest imaging. If necessary, levels such as arterial oxygen pressure (PaO_2), arterial oxygen saturation (SpO_2), alveolar-arterial difference in oxygen tension ($A\text{-}aDO_2$), and diffusing capacity of the lungs for carbon monoxide (DL_{CO}) should be tested. ○ If any abnormalities are observed, administration of the drug should be discontinued, and appropriate measures such as steroid therapy should be adopted. ○ Before starting the treatment, the patient or his/her family should be provided with a full explanation of the risks of EGFR-TKIs, including in particular, the initial symptoms of interstitial pneumonia and the fact that there have been fatal cases, and the patient should be instructed to contact a medical institution immediately if initial symptoms appear.

4. Case summary

Case 1

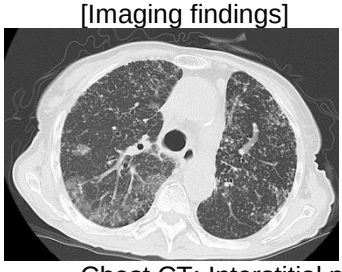
No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
1	Male 60s	EGFRT790M Mutation-positive non-small cell lung cancer [adenocarcinoma, stage IV] (hepatic function disorder)	osimertinib mesilate 80 mg 7 days	**ILD** Medical history: suspected ILD and drug-induced lung disorder in administration of afatinib; Smoking history: none History of lobectomy: yes; Oxygen therapy: yes (1-2 L/minute), PS=1 before administration, Albumin (Alb): 2.3g/dL before administration Approximately 17 years before administration Left lower lobectomy was performed. From approximately 13 years to approximately 2 years before administration Gefitinib (first-line therapy) was administered, followed by chemotherapy (second to fifth-line therapy). Approximately 1 year before administration During administration of afatinib (sixth-line therapy), drug-induced lung disorder was observed, and administration was discontinued. After steroid therapy, drug-induced lung disorder remitted. Treatment with chemotherapy, gefitinib, and then nivolumab (ninth-line therapy) was administered.

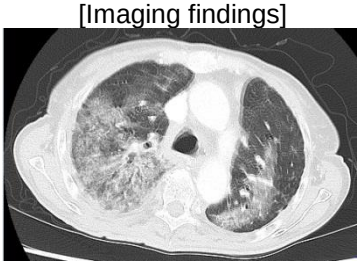
				[Imaging findings] Chest CT: During administration of afatinib, punctiform shadows appeared in both lung fields. 31 days before administration Disease progression was observed, and administration of nivolumab was discontinued. [Imaging findings] Chest X-ray: Lung cancer shadows were tending to aggravate. 17 days before administration The patient made a visit with pyrexia and malaise, and was admitted, diagnosed as pneumonia accompanied by respiratory failure. With antimicrobial treatment, pyrexia subsided, and both respiratory symptoms and inflammatory symptoms were recovering. [Imaging findings]  Chest CT: Findings including multiple nodular shadows due to lung cancer, ground-glass opacity thought to be due to lymphangiosis carcinomatosa, infiltrative shadows, and pleural effusion were observed, and thus shadows due not only to pneumonia but also to lung cancer, the underlying disease were observed. After treatment, (plain) chest X-ray photography showed that findings were resolving to a certain extent. 8 days before administration [Imaging findings]  Chest CT: Mainly in the lower left lung, dense infiltrative shadows accompanied by air bronchograms, countless nodular shadows in both lungs, and bilateral pleural effusion that was stronger on the right side. 5 days before administration Pyrexia recurred. Pneumonia was assumed, and antimicrobial treatment was resumed. Pyrexia subsequently subsided and inflammatory findings also decreased. On the other hand, abdominal pain due to metastases to the liver aggravated, and pleural effusion due to cancer and ascites due to peritoneal dissemination also increased, and thus, generally, lung cancer rapidly aggravated. Liver biopsy was positive for Ex19del and T790M mutations. [Imaging findings] Chest X-ray: Shadows remained present, mainly in the lower left lung. Multiple lung lesions. 3 days before administration [Imaging findings] Chest X-ray: bilateral multiple nodular shadows, infiltrative shadows in the middle and lower

				left lung fields, right pleural effusion. Day 1 of administration Osimertinib was started as tenth-line therapy (80 mg/day). After the start of administration Body weight had increased by at least 3 kg due to pleural effusion and ascites, but decreased after the start of administration. Day 5 of administration [Imaging findings] Chest X-ray: Multiple nodular shadows had shrunk slightly, infiltrative shadows of the middle and lower left lung fields had enlarged, and right pleural effusion was present. Day 8 of administration (day of discontinuation) Reassessment, including CT, was performed. Considering the possibility of non-infectious, including drug-induced, diseases, osimertinib was discontinued. (the final date of administration was day 7.) The patient's respiratory state was unchanged, requiring oxygen therapy at approximately 1-2 L, pyrexia was absent, and symptoms were stable. Therefore osimertinib was discontinued, the antimicrobial agent was changed, and diuretics were additionally administered to treat pulmonary oedema. [Imaging findings]  Chest CT: Infiltrative shadows had enlarged throughout the entire left lung and ground-glass shadows had enlarged in part of the right upper lobe. Pericardial effusion was present, and there was no change in pleural effusion. Bilateral multiple nodular shadows had shrunk markedly. Chest X-ray: Infiltrative shadows had enlarged to the entire left lung and ground-glass shadows had enlarged in part of the right upper lobe. Bilateral nodular shadows had shrunk markedly. There was no change in pleural effusion, and pericardial effusion appeared. 2 days after discontinuation During the day, there were no symptoms, and there was no change in respiratory state. 3 days after discontinuation Early in the morning, the patient complained of dyspnoea, and respiratory state aggravated. High-flow oxygen therapy and steroid pulse therapy (methylprednisolone 1 g/day) were started. From the evening, ventricular tachycardia was frequent, respiratory state further aggravated. [Imaging findings] Chest X-ray: Infiltrative shadows over all lung fields and suspected bilateral pleural effusion. Bilateral diffuse infiltrative shadows and increased inflammatory response were observed. 4 days after discontinuation In the early morning, the patient died. Autopsy: not

				performed.
	Concomitant medications: tramadol hydrochloride/acetaminophen combined drug, etodolac			

Case 2

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
2	Female 80s	EGFRT790M Mutation-positive non-small cell lung cancer (goitre, hypertension, type 2 diabetes mellitus, angina pectoris)	osimertinib mesilate 80 mg 11 days	**Interstitial pneumonia** Medical history: gastric surgery, gastric cancer; Smoking history: none History of lung surgery (left lower lobectomy + partial lingulectomy) and whole-brain irradiation: present; PS=1 before administration, Alb: 3.0 g/dL before administration. 1 year and 8 months before administration Non-small cell lung cancer (left lower lobe lung adenocarcinoma stage IIIA [T2N2M0]) was diagnosed. 1 year and 7 months before administration Left lower lobectomy + partial partial lingulectomy were performed. As the patient was elderly, no additional treatment was provided. 1 year and 2 months before administration [Imaging findings] Positron emission tomography (PET) CT: Recurrence found (metastases to hilar mediastinal lymph nodes). From 1 year and 2 months to 5 months before administration Gefitinib was administered (result: tending towards partial response [PR]). From 4 months to 56 days before administration Pemetrexed was administered (result: stable disease [SD]). From 58 to 29 days before administration Nivolumab was administered (3 mg/kg). Approximately 50 days before administration Because of a complaint by the patient (tightness of the face), a head magnetic resonance imaging (MRI) scan was performed, and multiple metastases to the brain were observed. From 44 to 21 days before administration Whole-brain irradiation was performed. 10 days before administration Bronchoscopy found intrapulmonary metastases. T790M mutation: present. From images, interstitial pneumonia was pointed out, and from the results of bronchoscopic biopsy, alveolar type II epithelial enlargement and increase was present but no obvious ILD findings were found, and it was not judged that ILD was present. [Imaging findings]  Chest CT: Interstitial pneumonia

				Day 1 of administration At fourth-line therapy, administration of osimertinib 80 mg/day was started. Day 4 of administration Shortness of breath was present, and administration of oxygen at 1 L/minute was started. Day 9 of administration D-dimer increased, and as a state leading to disseminated intravascular coagulation was suspected, heparin was administered. Angiography: no embolism. Day 10 of administration Oxygen was increased to 3 L/minute. Day 12 of administration (day of discontinuation) Interstitial pneumonia was diagnosed, and osimertinib was discontinued (the final dose was on day 11 of administration). [Imaging findings]  Chest X-ray: shadows present. Chest CT: Lung cancer tending to shrink, ground-glass shadows found. 1–3 days after discontinuation Steroid pulse therapy was administered (methylprednisolone 1000 mg × 3 days). 4 days after discontinuation Prednisolone was administered (40 mg) and respiratory discomfort appeared. Oxygen was administered at 15 L/minute. 5 days after discontinuation The patient died. Autopsy performed: no.
	Concomitant medications: losartan potassium, voglibose, nicorandil, betamethasone, vonoprazan fumarate, tulobuterol, etodolac, hochuekkito, loxoprofen sodium hydrate			

5. Request for cooperation with adverse drug reaction reports

At present, it is unclear whether the extended use of EGFR-TKIs following the administration of nivolumab increases the risk of ILD. Nonetheless, MHLW and PMDA plan to continue to pay attention to the safety in use. If ILD occurs after administration of EGFR-TKI, please report ADR information, including the treatment history for the relevant patient, and the history of use of drugs such as nivolumab.

<References>

(1) Precautions relating to ILD during administration of EGFR-TKIs (request) (Pharmaceutical Safety and Environmental Health Bureau [PSEHB] Notification No. 0722-3 and 4, dated July 22, 2016)
(2) Related AstraZeneca K.K. website: MediChannel, AstraZeneca's information website for healthcare professionals
http://med.astrazeneca.co.jp/safety/TAG.html (only available in Japanese language)
(3) Related Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb K.K. website: Opdivo.jp

https://www.opdivo.jp (only available in Japanese language)

(4) Japanese Society of Medical Oncology: About interstitial pneumonia occurring in patients who have been administered EGFR-TKIs following nivolumab (Opdivo®)
http://www.jsmo.or.jp/news/jsmo/2060713.html (only available in Japanese language)

2

Genome Research Relating to Drug-induced Serious Skin Disorders

1. Introduction

Of the various ADRs, those that are not based on pharmacological effects are generally difficult to predict onset and, in many cases, tend to be severe and require treatment after the onset. However, since 2004, potential predictors have been reported through the exploration of genomic information related to their onset. The MHLW as well as the National Institute of Health Sciences (NIHS) are currently collecting genomic samples and clinical information about patients who have developed ADRs related to skin disorders (Stevens-Johnson syndrome [oculomucocutaneous syndrome; SJS] and toxic epidermal necrolysis [TEN]), rhabdomyolysis, and ILD. Research is underway through analysis of the gathered information to realize prediction and prevention style safety measures for ADR through the use of genomic information. As of the end of March 2016, a total of 299 cases of skin disorders, 180 cases of rhabdomyolysis (muscle disorder), and 156 cases of ILD have been collected. The results for skin disorder, for which research is particularly advanced, have been summarized in this section.

2. Stevens-Johnson syndrome (oculomucocutaneous syndrome; SJS) and toxic epidermal necrolysis (TEN)

SJS is characterized by severe enanthema and skin erythema in the mucocutaneous junctions such as the lips, conjunctiva of the eyes, and the vulva accompanied by pyrexia (38°C or above). Necrotic epidermal disorders, such as blisters and epidermal detachment, are often noted. SJS is considered to be caused mainly by drugs. In contrast, TEN is characterized by extensive erythema, marked necrotic epidermal disorders such as blisters, epidermal detachment, and erosion over 10% of the entire body surface, and accompanied by pyrexia (38°C or above) and enanthema. It is considered the most serious drug-induced skin disorder[1)]. Although the occurrence frequency of SJS and TEN is extremely low such as 1–6 and 0.4–1.2 individuals per million/year, respectively, once they occur, they can be associated with a poor prognoses, and disorders of eyes, respiratory tract, etc. may remain even after skin symptoms have improved [2), 3)].

3. Results of Genomic Research on SJS/TEN

3.1 Allopurinol-induced SJS/TEN

With regards to allopurinol, a treatment for hyperuricemia, a significant association with a type of human leukocyte antigen (HLA), *HLA-B*58:01*, was observed with odds ratio of 62.8 [4)], and this association has been noted in package inserts. The association was first reported in Han Chinese, and was later observed among Japanese, Thai, Caucasians, and Koreans as well. Furthermore, analysis was conducted on genome-wide patterns of genetic polymorphisms to explore related genetic polymorphisms besides *HLA* type, but no other markers besides *HLA-B*58:01* could be identified. On the other hand, genetic polymorphism absolutely linked with this *HLA* type was identified (rs9263726) and genotyping for this was developed using polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) techniques [5)]. The prevalence of *HLA-B*58:01* among the general Japanese population

is approximately 1% [6].

3.2 Carbamazepine-induced SJS/TEN

With regards to carbamazepine, an anti-epileptic treatment, an extremely strong association with *HLA-B*15:02* was reported with odds ratio 1 357 among Han Chinese as already introduced in past Pharmaceutical and Medical Devices Safety Information (PMDSI) [7], and this association has later been confirmed in Thai, Indian and Malay individuals as well. However, no carriers of *HLA-B*15:02* was confirmed among Japanese patients who developed SJS/TEN. Instead, an association with *HLA-B*15:11* was demonstrated [8]. In addition, association with *HLA-A*31:01* was reported based on analysis of Caucasians and Japanese individuals, and this association has been noted in package inserts [9, 10]. These associations were confirmed as well in the most recent results where the number of cases with SJS/TEN onset included 21 individuals. The odds ratio for the significant association with *HLA-B*15:11* was 12.2, and the odds ratio for the association with *HLA-A*31:01* was 3.72 [11]. Both *HLA-B*15:02* and *HLA-B*15:11* belong to the same serotype HLA-B75, and it is considered that which type SJS/TEN is related to depends on the frequency of the applicable *HLA* type in each ethnicity group. Furthermore, in an *In vitro* study conducted in Taiwan, B75 molecules were reported to directly bind with carbamazepine non-covalently and thereby activate cytotoxic T cells derived from patients who developed SJS/TEN due to the use of carbamazepine, which then destroy HLA-B75 positive cells. This is presented as molecular evidence for involvement of HLA-B75 molecules in the onset of SJS/TEN [12].

3.3 Phenobarbital-induced SJS/TEN

Although based on a limited sample size, analysis among 8 patients who developed SJS/TEN due to the use of phenobarbital, an anti-epileptic treatment, demonstrated a significant association with *HLA-B*51:01* (odds ratio: 16.71) [13].

3.4 Zonisamide-induced SJS/TEN

Analysis among 12 patients who developed SJS/TEN due to the use of zonisamide, an anti-epileptic treatment, demonstrated a significant association with *HLA-A*02:07* (odds ratio: 9.77) [13].

3.5 Phenytoin-induced SJS/TEN

Analysis was conducted collaboratively with Taiwan and Malaysia for phenytoin, an anti-epileptic treatment. It first demonstrated a significant association between onset of severe drug eruptions (SJS/TEN, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome [DRESS/DIHS]) and *CYP2C9*3* (1075A>C, Ile359Leu), a defunctioning polymorphism in CYP2C9, an enzyme for detoxication metabolism of phenytoin. Furthermore, a significant association with odds ratio 8.88 was demonstrated among Japanese SJS/TEN patients [14]. In addition, the actual association was also validated among Malay patients with SJS/TEN or DRESS. It has also been demonstrated in actual practice that blood concentration of phenytoin is significantly higher among patients with severe drug eruptions compared to the control phenytoin resistant patients. The prevalence of *CYP2C9*3* among Japanese is approximately 5-6% [6]

3.6 Antipyretic and analgesic-induced SJS/TEN

Analysis of patients who developed SJS/TEN accompanied with severe eye disorder after use of antipyretics and analgesics for common cold symptoms demonstrated a significant association with *HLA-A*02:06* and *HLA-B*44:03* (with odds ratio 5.18 and 4.22, respectively)[15]. The prevalence of *HLA-A*02:06* and *HLA-B*44:03* among Japanese is approximately 14% for both markers[15]. This analysis is regarded as validated by the consistent analysis results conducted by Professor Kinoshita, Associate Professor Ueda, and others from Kyoto Prefectural University of Medicine targeting patients diagnosed with SJS/TEN accompanied with eye disorders due to common cold preparations.

Based on analysis among incidents of ocular mucosal disorders noted in the case reports for collected specimens, acetaminophen was suggested to be a suspected drug with significant incidence of pseudomembrane formation or eye damage more severe than erosion or loss of corneal epithelium (odds ratio: 3.27). Furthermore, results indicated a significantly higher ratio of severe ocular mucosal disorder when acetaminophen was administered for common cold symptoms rather than when it was administered for cases other than common cold symptoms (odds ratio: 13.0) [16].

4. Conclusions

The above provides an overview of the genomic analysis results, etc. with regards to SJS/TEN obtained by the NIHS. Some drugs have a limited number of cases even though results have been published as papers, and, in many cases, many of patients carrying genotypes associated with high risk do not actually suffer from onset. Therefore, it is currently difficult in most cases to use these results immediately in clinical practice to avoid severe drug eruptions in pharmacological treatment. However, if the usefulness of these results is demonstrated in future validation analysis, etc., this may become the basis for clinical application.

The ADRs addressed in this research have low incidence but can be life-threatening. In addition, given that different factors associated with onset of these ADRs have been identified depending on ethnicity, it is extremely important to gather information on Japanese cases with these ADRs so as to gain useful analytical results to predict onset.

This research is being conducted with cooperation from the Federation of Pharmaceutical Manufacturers' Associations of Japan and each MAH as well as healthcare professionals and patients. Healthcare professionals are encouraged to continue cooperating with this research in addition to providing information to the PMDA or MAH of suspected drugs when development of skin disorder (SJS/TEN), rhabdomyolysis, or ILD is confirmed among patients after administration of drugs. Such cooperation is essential in advancing prediction and prevention style safety measures through further accumulation of such findings.

Genomic Research Results on Severe Drug Eruptions Conducted by NIHS

HLA type (genotype)	Japanese health subjects	SJS/TEN patients		Odds ratio (95% confidence interval)	P-value
	Allele frequency	Carrier incidence (sensitivity)	Allele frequency		
Allopurinol (antiuricemic drug)					
*B*58:01*[4]	0.6%	10/18 (55.6%)	10/36 (27.8%)	62.8 (21.2-185.8)	5.4×10^{-12}
Carbamazepine (antiepileptic drug)					
*B*15:11*	1.0%	5/21 (23.8%)	5/42 (11.9%)	12.2 (4.6-32.1)	0.0001
*A*31:01*[11]	8.7%	9/21 (42.9%)	10/42 (23.8%)	3.72 (1.56-8.88)	0.004
Phenobarbital (antiepileptic drug)					
*B*51:01*[13]	7.87%	6/8 (75.0%)	7/16 (43.8%)	16.71 (3.66-83.06)	0.0003
Zonisamide (antiepileptic drug)					
*A*02:07*[13]	3.49%	5/12 (41.7%)	5/24 (20.8%)	9.77 (3.07-31.1)	0.0008
Phenytoin (antiepileptic drug)					
*CYP2C9*3*[14]	5.33% (Carriers)	3/9 (33.3%)		8.88 (2.20-35.83)	0.003
Antipyretics and analgesics					
*A*02:06*[15]	13.6% (Carriers)	9/20 (45.0%)		5.18 (1.98-13.56)	0.0014
*B*44:03*[15]	13.6% (Carriers)	8/20 (40.0%)		4.22 (1.59-11.19)	0.0058

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3
Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated August 4, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Olanzapine

Brand name (name of company)	a. Zyprexa Tablets 2.5 mg, 5 mg, 10 mg, Zyprexa Zydis Tablets 2.5 mg, 5 mg, 10 mg, Zyprexa Fine Granules 1% (Eli Lilly Japan K.K.) and others b. Zyprexa Intramuscular Injection 10 mg (Eli Lilly Japan K.K.)
Therapeutic category	Psychotropics
Indications	a. Schizophrenia Improvement of manic and depressive symptoms in bipolar disorder b. Psychomotor excitability in schizophrenia

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	**Drug-induced hypersensitivity syndrome (DIHS):** Rash and/or pyrexia may occur as initial symptoms, followed by serious late-onset hypersensitivity symptoms with hepatic function disorder, lymphadenopathy, increased white blood cell count, increased eosinophil count, atypical lymphocytes, etc. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be adopted. The reactivation of viruses including Human Herpes Virus 6 (HHV-6) has been frequently found to be associated with DIHS. Symptoms, such as rash, pyrexia, and/or hepatic function disorder, may relapse or be prolonged even after the discontinuation of administration and, therefore, caution should be exercised.
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 2 months (April 2013 to June 2016). Cases related to DIHS: 1 case (no fatal case) The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 730 000 Launched in Japan: June 2001

Case summary

No.	Patient		Daily dose	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 10s	Mixed disorders of conduct and emotions* (Asthma, irritability)	2.5 mg for 37 days	**DIHS** 14 days before administration Treatment with risperidone 1 mg/day was initiated for irritability. Day 1 of administration Treatment with olanzapine 2.5 mg, carbamazepine 400 mg, and brotizolam 0.25 mg was initiated for mixed disorders of conduct and emotions.

				30 days after administration The patient suffered from pyrexia, 38°C and higher, and diarrhoea. Non-pyrine common cold preparations, acetaminophen, and loxoprofen sodium hydrate was administered to treat pyrexia and common cold symptoms. 34 days after administration (Day of onset) Rapid onset of fever over 40°C and erythema mainly on the patient's torso. Abnormal hepatic function and increase in Eos (numerical values unknown) were confirmed. Administration of carbamazepine, brotizolam, non-pyrine common cold preparations, acetaminophen and loxoprofen sodium hydrate was discontinued. 36 days after administration The patient was referred to a dermatologist in the hospital. 38 days after administration (Day of discontinuation) Rash on the upper limbs spread to the forearm and disseminated erythema was confirmed on the torso and lower limbs. Redness was found in the oral cavity, hard palate, pharynx, and buccal mucosa. Petechiae was observed in the hard palate. Bulbar conjunctiva hyperaemia was not seen. Treatment with oral prednisolone was initiated. Pyrexia over 40°C persisted and CT was conducted to diagnose the source of the fever. Thickening of the gallbladder wall was confirmed; therefore, a gastroenterologist was consulted. The patient was admitted to the hospital and placed under observation as increase in liver enzymes was not drastic. Administration of olanzapine was discontinued. 5 days after discontinuation Dosage of prednisolone was increased to 1.0 mg/kg/day. 6 days after discontinuation Rash was resolving. Given that conditions were not consistent with reactivation of HHV-6 immunoglobulin (Ig G), the patient was diagnosed to have atypical DIHS. Administration of risperidone was discontinued. 8 days after discontinuation Skin biopsy was conducted. The clinical diagnosis was toxicoderma; in terms of clinical findings, no apparent abnormalities were observed on the epidermis but liquefaction degeneration was confirmed in the basal epidermal layer. Infiltration of inflammatory cells, mainly lymphocytes, in association to erythrodiapedesis was observed in microvessels of upper dermis and around the adnexa. Infiltration of Eos stood out slightly. The findings did not contradict the clinical diagnosis. There were no malignant findings. HHV-6 IgG (fluorescent antibody [FA] staining) was 160 times. 11 days after discontinuation Specific IgE measurements were conducted. The patient was identified to have the following allergies: cat dander, Phleum pratense, Dactylis glomerata, Cryptomeria, and Chamaecyparis obtusa. 31 days after discontinuation Drug-induced lymphocyte stimulation test was conducted and all results were negative. Criteria for assessment for Stimulation index (S.I.) 180% or less: negative, 181% or more: positive Carbamazepine (measured value: 2038 cpm, S.I.: 171%) Olanzapine (measured value: 1950 cpm, S.I.: 164%) Non-pyrine common cold preparations (measured value:

				989 cpm, S.I.: 83%) Loxoprofen sodium hydrate (measured value: 2076 cpm, S.I.: 174%) Acetaminophen (measured value: 1112 cpm, S.I.: 93%) Brotizolam (measured value: 1490 cpm, S.I.: 125%) Risperidone (measured value: 1145 cpm, S.I.: 96%) Control (measured value: 1187 cpm) 32 days after discontinuation Residual erythrosis in lower limb nodules, but conditions were resolving as some portions were dried. The patient was discharged from the hospital. 46 days after discontinuation Consultation on an out-patient basis. No relapse seen in rash.
	Concomitant medications: Carbamazepine, brotizolam, risperidone, non-pyrine cold preparations, acetaminophen, loxoprofen sodium hydrate			

Laboratory examination

Test item/ Test date	34 days after adminis-teration (day of onset)	Day of discontin-uation	3 days after discontin-uation	4 days after discontin-uation	6 days after discontin-uation	8 days after discontin-uation	31 days after discontin-uation	46 days after discontin-uation
WBC (/μL)		10950	15810	20010	32850	23090	10210	6560
Neutrophil (%)							65.4	
Lymphocyte (%)		18.0	22.0	30.0	18.0	16.0	25.1	
Abnormal lymphocyte (%)		10.0	11.0	2.0	5.5	5.0		
Monocyte (%)		7.0	7.0	4.0	3.5	4.5	6.1	
Eos (%)	Increased	17.0	27.0	27.0	21.5	11.5	2.9	
Basophil (%)		1.0	1.0	0.0	0.5	0.5	0.5	
Total bilirubin (mg/dL)		0.62	0.46	0.47	0.53	0.44	1.89	2.19
Direct bilirubin (mg/dL)			0.10	0.10	0.09	0.07	0.20	0.27
AST/GOT (IU/L)	39	52	55	39	23	21	14	17
ALT/GPT (IU/L)	58	62	102	97	80	64	33	20
LDH (IU/L)		478	477	523	742	647	226	191
ALP (IU/L)		437	405	382	353	338	204	195
γ−GTP (IU/L)		217	188	163	124	105	47	24
CRP (mg/dL)	6.01	6.1	1.4	1.4	1.1	0.3	0.0	0.0
EBV EBNA (FA) Normal range (less than 10)		Less than 10						
EBV VCA IgM (FA) Normal range (less than 10)		Less than 10						
CMV IgG (EIA) Normal range (less than 2.0)		0.3(-)						
CMV IgM (EIA) Normal range (less than 0.8)		0.33(-)						
HHV-6 IgG (FA) Normal range (less than 10)						160	160	
HHV6 DNA quantitative						2.0×10*1 or less		
ANA quantitative Reference value (less than 40)		-/Less than 40						
Anti-mitochondria Reference value (less than 20)		-/Less than 20						
4-type collagen Normal range (150 ng/mL or less)		123						

2 Azosemide

Brand name (name of company)	Diart Tablets 30 mg, 60 mg (Sanwa Kagaku Kenkyusho Co., Ltd.), and others
Therapeutic category	Diuretics
Indications	Cardiac-induced edema (congestive cardiac failure), renal-induced edema, and hepatic-induced edema

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Agranulocytosis and leukopenia: Agranulocytosis or leukopenia may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

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 2 months (April 2013 to June 2016)

Cases related to agranulocytosis and/or leukopenia: 2 cases (0 fatal cases)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 470 000

Launched in Japan: July 1987

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 90s	Chronic renal failure (fluid retention due to chronic renal failure, bronchial asthma, iron deficiency anaemia, nephrogenic anaemia, hypocalcaemia, hypokalaemia)	60 mg for 6 days	**Agranulocytosis** 20 days before administration The patient with a chief complaint of dyspnoea was admitted to the hospital. Administration of panipenem/betamipron injection was initiated for the treatment of pneumonia. While the patient had end-stage chronic renal failure, dialysis was not used and the patient was treated with fluid replacement, erythropoiesis stimulating agents, and iron preparations. 2 days before administration The patient was suspected to have bacterial pneumonia. Recovering pneumonia was confirmed using a chest CT scan. Day 1 of administration Administration of azosemide was initiated for the purpose of resolving fluid retention associated to chronic renal failure. WBC count was 5200/mm^3 (neutrophil count was 3556/mm^3). Day 4 of administration WBC decreased to 1700/mm^3 (neutrophil count: 736/mm^3). Day 6 of administration (Day of discontinuation) Onset of agranulocytosis. WBC was 700/mm^3 (neutrophil count: 81/mm^3). Administration of azosemide was discontinued. 100 mg of lenograstim (genetical recombination) was administered for 3 days. In addition, panipenem/betamipron 0.5 g/day, povidone-iodine, and amphotericin B syrup was administered as prophylaxis for infections. 2 days after discontinuation

				Agranulocytosis resolved. WBC was 2200/mm^3 (neutrophil count: 1397/mm^3). 3 days after discontinuation WBC resolved to 5800/mm^3 (neutrophil count: 4506/mm^3).
	Concomitant medications: Tulobuterol, panipenem/betamipron, alfacalcidol, ferrous fumarate, epoetin beta pegol (genetical recombination)			

Laboratory examination

Test item	20 days before admin-istration	7 days before admin-istration	4 days before admin-istration	Day 1 of admin-istration	Day 4 of admin-istration	Day 6 of admin-istration (Day of discontin-uation)	2 days after discontin-uation	3 days after discontin-uation	5 days after discontin-uation	11 days after discontin-uation
WBC (/mm^3)	12200	8100	7000	5200	1700	700	2200	5800	5500	8000
Hemoglobin (g/dL)	8.9	-	9.7	9.2	8.7	8.8	9.2	8.6	9.5	8.2
Platelets (/mm^3)	-	-	168000	142000	192000	242000	230000	243000	242000	259000
Neutrophils (/mm^3)	-	-	5817	3556	736	81	1397	4506	4136	6528
Neutrophil (%)	-	-	83.1	68.4	43.3	11.7	63.5	77.7	75.2	81.6
Lymphocyte (%)	-	-	8.6	20.0	38.6	53.6	21.4	11.1	13.2	13.6
Monocyte (%)	-	-	2.3	6.0	15.7	33.3	14.3	10.8	11.0	4.5
Eos (%)	-	-	5.7	5.2	1.8	0.0	0.4	0.2	0.4	0.1
Basophil (%)	-	-	0.3	0.4	0.6	1.4	0.4	0.2	0.2	0.2
CRP (mg/dL)	17.89	6.71	-	4.23	2.29	-	3.89	-	1.49	0.14

4

Revision of Precautions (No. 277)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated August 4, 2016.

1

Antineoplastics – Miscellaneous

(1) Imatinib mesilate, (2) Dasatinib hydrate

Brand name	(1) Glivec Tablets 100 mg (Novartis Pharma K.K.), and others (2) Sprycel Tablets 20 mg, 50 mg (Bristol-Myers Squibb K.K.)
Important precautions	Reactivation of hepatitis B virus may occur among hepatitis B virus carriers or patients who have a history of being infected (i.e. HBs antigen negative and HBc antibody or HBs antibody positive) following administration of Bcr-Abl tyrosine kinase inhibitors. The presence or absence of hepatitis B virus infection should be confirmed prior to administrating this drug and appropriate measures should be adopted before the administration of this drug. After beginning the administration of this drug, attention should be paid to the occurrence of signs or symptoms related to reactivation of the hepatitis B virus through continuous hepatic function tests, monitoring of hepatitis virus markers, etc.
Adverse reactions (clinically significant adverse reactions)	Infections: Infections such as pneumonia and sepsis may occur. Reactivation of hepatitis B virus may also occur. Patients should be carefully monitored through periodic blood test, etc. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be adopted.

2 **Antineoplastics – Miscellaneous**

Nilotinib hydrochloride hydrate

Brand name (name of company)	(3) Tasigna Capsules 150 mg, 200 mg (Novartis Pharma K.K.)
Therapeutic category	Antineoplastics – Miscellaneous
Indications	(3) Chronic myeloid leukaemia in chronic or accelerated phase
Brand name	Tasigna Capsules 150 mg, 200 mg (Novartis Pharma K.K.)
Important precautions	Reactivation of hepatitis B virus may occur among hepatitis B virus carriers or patients who have a history of being infected (i.e. HBs antigen negative and HBc antibody or HBs antibody positive) following administration of Bcr-Abl tyrosine kinase inhibitors. The presence or absence of hepatitis B virus infection should be confirmed prior to administrating this drug and appropriate measures should be adopted before the administration of this drug. After beginning the administration of this drug, attention should be paid to the occurrence of signs or symptoms related to reactivation of the hepatitis B virus through continuous hepatic function tests, monitoring of hepatitis virus markers, etc.
Adverse reactions (clinically significant adverse reactions)	Infections: Infections such as pneumonia and sepsis may occur. Reactivation of hepatitis B virus may also occur. Patients should be carefully monitored through periodic blood test, etc. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be adopted.

3 **Antineoplastics – Miscellaneous**

Bosutinib hydrate

Brand name	Bosulif Tablets 100 mg (Pfizer Japan Inc.)
Important precautions	Reactivation of hepatitis B virus may occur among hepatitis B virus carriers or patients who have a history of being infected (i.e. HBs antigen negative and HBc antibody or HBs antibody positive) following administration of Bcr-Abl tyrosine kinase inhibitors. The presence or absence of hepatitis B virus infection should be confirmed prior to administrating this drug and appropriate measures should be adopted before the administration of this drug. After beginning the administration of this drug, attention should be paid to the occurrence of signs or symptoms related to reactivation of the hepatitis B virus through continuous hepatic function tests, monitoring of hepatitis virus markers, etc.

4 **Chemotherapeutics-Synthetic antibacterials**

Sitafloxacin hydrate

Brand name	Gracevit Tablets 50 mg, Gracevit Fine Granules 10% (Daiichi Sankyo Company, Limited)
Adverse Reactions (clinically significant adverse reactions)	**Thrombocytopenia:** Thrombocytopenia may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted. **Psychiatric symptoms including confusion, delirium, and hallucination:** Psychiatric symptoms including confusion, delirium, and hallucination may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

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 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 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 July 31, 2016)
◎: Products for which EPPV was initiated after July 1, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Vigabatrin Sabril 500mg Powder	Sanofi K.K.	July 27, 2016
◎	Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide Fumarate Genvoya Combination Tablets	Japan Tobacco Inc.	July 8, 2016
	Octocog Beta (Genetical Recombination) Kovaltry for iv injection 250, 500, 1000, 2000, 3000	Bayer Yakuhin, Ltd.	June 29, 2016
	Bexarotene Targretin Capsules 75 mg	Minophagen Pharmaceutical Co., Ltd.	June 23, 2016
	Maxacalcitol/betamethasone butyrate propionate Marduox Ointment	Chugai Pharmaceutical Co., Ltd.	June 21, 2016
	Primaquine Phosphate Primaquine Tablets 15 mg	Sanofi K.K.	June 17, 2016
	Dutasteride (1) Zagallo Capsules 0.1 mg (2) Zagallo Capsules 0.5 mg	GlaxoSmithKline K.K.	June 13, 2016
	Mepolizumab (Genetical Recombination) Nucala for Subcutaneous Injection 100 mg	GlaxoSmithKline K.K.	June 7, 2016
	Radium (^{223}Ra) Chloride Xofigo Injection	Bayer Yakuhin, Ltd.	June 1, 2016
	Rurioctocog Alfa Pegol (Genetical Recombination) Adynovate Intravenous 250, 500, 1000, 2000	Baxalta Japan Ltd.	June 1, 2016
	Trametinib Dimethyl Sulfoxide Mekinist Tablets 0.5mg, 2mg	Novartis Pharma K.K.	June 1, 2016
	Dabrafenib Mesilate Tafinlar Capsules 50mg, 75mg	Novartis Pharma K.K.	June 1, 2016

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
Perampanel Hydrate Fycompa Tablets 2 mg, 4 mg	Eisai Co., Ltd.	May 26, 2016
Asenapine Maleate Sycrest Sublingual Tablets 5 mg, 10 mg	Meiji Seika Pharma Co., Ltd.	May 26, 2016
Sebelipase Alfa (Genetical Recombination) Kanuma Injection for Intravenous 20 mg	Alexion Pharma G.K.	May 25, 2016
Osimertinib Mesilate Tagrisso Tablets 40 mg, 80 mg	AstraZeneca K.K.	May 25, 2016
Ceritinib Zykadia Capsules 150 mg	Novartis Pharma K.K.	May 25, 2016
Ibrutinib Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	May 25, 2016
Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg*1	Teijin Pharma Limited	May 23, 2016
Botulinum Toxin Type A Botox Vista Injection 50 Units*2	Allergan Japan K.K.	May 23, 2016
Iloprost Ventavis Inhalation Solution 10 μg	Bayer Yakuhin, Ltd.	May 16, 2016
Methacholine Chloride (1) Provocholine Powder for Inhalation Solution 100 mg (2) Kenbran Powder for Inhalation Solution 100 mg	(1) Sanwa Kagaku Kenkyusho Co., Ltd. (2) Santen Pharmaceutical Co., Ltd.	May 10, 2016
Nonacog Gamma (Genetical Recombination) Rixubis Intravenous 250, 500, 1000, 2000, 3000	Baxter Limited	May 9, 2016
Luliconazole Luconac Solution 5% *3	Sato Pharmaceutical Co., Ltd.	April 25, 2016
Progesterone Luteum Vaginal Suppository 400 mg	Aska Pharmaceutical Co., Ltd.	April 21, 2016
Evolocumab (Genetical Recombination) Repatha SC Injection 140 mg syringe, 140 mg pen	Amgen Astellas BioPharma K.K.	April 21, 2016
Ibandronate Sodium Hydrate Bonviva Tablets 100 mg	Chugai Pharmaceutical Co., Ltd.	April 21, 2016
Duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg *4	Shionogi & Co., Ltd.	March 18, 2016
Eribulin Mesilate Halaven Intravenous Injection 1 mg*5	Eisai Co., Ltd.	February 29, 2016
Risperidone Risperdal Tablets 1 mg, 2 mg, Fine Granules 1 %, Risperdal OD Tablets 0.5 mg 1 mg, 2 mg, Risperdal Oral Solution 1 mg/mL *6	Janssen Pharmaceutical K.K.	February 29, 2016
Rituximab (Genetical Recombination) Rituxan Injection 10 mg/mL*7	Zenyaku Kogyo Co., Ltd.	February 29, 2016
Progesterone Utrogestan vaginal capsules 200mg	Fuji Pharma Co., Ltd.	February 18, 2016

*1 Hyperuricemia associated with cancer chemotherapy

*2 Lateral canthal lines in adult patients under the age of 65

*3 Nail tinea

*4 Pain associated with chronic lumbago

*5 Malignant soft tissue sarcoma

*6 Irritability associated with autism spectrum disorder in childhood

*7 Prophylaxis of antibody-related type rejection in the ABO blood group incompatibility transplant of kidney and liver transplants