Pharmaceuticals and Medical Devices Safety Information

No. 372 April 2020

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Available information is listed here.

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No. 372 April 2020

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

[Outline of Information]

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
DIHS	Drug induced hypersensitivity syndrome
HLA	Human leukocyte antigen
ILD	Interstitial lung disease
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
NAT2	N-acetyltransferase 2
NIHS	National Institute of Health Sciences
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PT-INR	Prothrombin time international normalized ratio
SJS	Stevens-Johnson Syndrome
TEN	Toxic epidermal necrolysis

1
Genome Research on Drug-related Severe Cutaneous Adverse Reactions

Introduction

Among various adverse drug reactions (ADRs), it is generally difficult to predict the onset of those that cannot be related to assumed pharmacological effects, and these ADRs tend to be severe, requiring treatment after the onset. However, genetic factors related to the onset of such ADRs have been reported as genome analysis advances. Research is underway at the MHLW and the National Institute of Health Sciences (NIHS) to achieve prediction and prevention style safety measures against ADRs through active use of such genomic information, by collecting and analyzing genomic samples and clinical information from patients who developed adverse reactions namely skin disorders (Stevens-Johnson Syndrome [oculomucocutaneous syndrome; SJS] and toxic epidermal necrolysis [TEN]), rhabdomyolysis, and interstitial lung disease (ILD). As of March 31, 2020, a total of 329 cases of SJS/TEN, 250 cases of rhabdomyolysis, and 230 cases of ILD samples has been collected. The table below summarizes the main achievements of the research projects on SJS/TEN which are making particularly good progress.

Major Results of Genome Research on Severe Drug Eruptions Conducted by NIHS

HLA type (genotype)	Japanese healthy volunteers	SJS/TEN patients		Odds ratio (95% confidence interval)	P-value
	Allele frequency	Carrier frequency (sensitivity)	Allele frequency		
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*	8.7%	9/21 (42.9%)	10/42 (23.8%)	3.72 (1.56-8.88)	0.004
Phenobarbital (antiepileptic drug)					
*B*51:01*	7.87%	6/8 (75.0%)	7/16 (43.8%)	16.71 (3.66-83.06)	0.0003
Zonisamide (antiepileptic drug)					
*A*02:07*	3.49%	5/12 (41.7%)	5/24 (20.8%)	9.77 (3.07-31.1)	0.0008
Allopurinol (antihyperuricemic drug)					
*B*58:01*	0.6%	10/18 (55.6%)	10/36 (27.8%)	62.8 (21.2-185.8)	5.4×10^{-12}
Phenytoin (antiepileptic drug)					
*CYP2C9*3*	5.33% (carriers)	3/9 (33.3%)		8.88 (2.20-35.83)	0.003
Antipyretics and analgesics					
*A*02:06*	13.6% (carriers)	9/20 (45.0%)		5.18 (1.98-13.56)	0.0014
*B*44:03*	13.6% (carriers)	8/20 (40.0%)		4.22 (1.59-11.19)	0.0058
Sulfonamide (antimicrobial drug)					
A11:01	16.9% (carriers)	6/8 (75.0%)		14.77 (2.97-73.4)	4.91×10^{-4}

2. Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)

SJS exhibits an extensive mucosal lesion, accompanied by pyrexia, on mucosal junctions such as the lip, ocular conjunctiva, and the vulva, etc. noted by erosion and blisters derived from necrotic epidermal disorders associated with diffuse erythema. The erosion and blisters extend over less than 10% of the body surface area. SJS is caused by drugs and also infections such as mycoplasma infection. TEN, on the other hand, shows an extensive erythema and marked necrotic epidermal disorders such as blisters, epidermal detachment, and erosion over 10% of the body surface area, with pyrexia and enanthema. It is considered the most serious drug-induced skin reaction. Although the incidence of SJS and TEN is extremely low such as 1-6 and 0.4-1.3 individuals per million/year, respectively, once they occur, they can be associated with poor prognoses, and disorders of eyes (such as pseudomembrane formation), respiratory tract, etc. may remain even after skin symptoms have improved.

Diagnostic criteria for the 2 types of adverse reactions were revised in 2016[1)] as well as their Manuals for Management of Individual Serious Adverse Drug Reactions[2, 3)] in 2017 as listed in the Reference.

Genome research on drug-related severe cutaneous adverse reactions was already described in the PMDSI No. 336[4)]. This section addresses drugs for which new knowledge has been obtained since then in our research and other sources (including overseas ones).

3. Results of genome research on SJS/TEN

3. 1 Allopurinol-related severe cutaneous adverse reactions

A significant association with a type of human leukocyte antigen (HLA), *HLA-B*58:01,* has beenobserved for allopurinol, a drug for hyperuricemia and this association is described in the package insert. First reported in Han Chinese, the association has been subsequently observed in Japanese, Thai, Caucasians, Koreans, etc. as well. The prevalence of *HLA-B*58:01* in the general Japanese population is approximately 1%. Exploration for other risk factors than HLA genotype is also progressing overseas. Allopurinol is excreted in the kidney, and renal disorder (especially with eGFR<30 mL/min/1.73 m^2) was identified as a risk factor by the result of a study conducted in Taiwan[5)]. Renal disorder was also reported in Thailand as a potential risk factor[6)].

3. 2 Carbamazepine-related SJS/TEN

For carbamazepine, an antiepileptic, associations between SJS/TEN and *HLA-B*15:11 or HLA A*31:01* have been reported in the Japanese population and the latter association is noted in the package insert. An association with *HLA-A*31:01* has also been reported for carbamazepine-related hypersensitivity syndromes (DRESS/DIHS) or even mild drug eruption. The prevalence of *HLA-B*15:11 and HLA-A*31:01* in the Japanese population has been reported to be approximately 1% and 8-9%, respectively, with the latter being higher. In a research paper published from Riken, Japan in 2018, 1 130 patients who were diagnosed to be administered carbamazepine were examined for *HLA-A*31:01* prior to administration. Patients who tested negative were administered carbamazepine and those who tested positive were administered an alternative drug. As a result, a 41-61% reduction in the incidence of carbamazepine-related drug eruption was observed demonstrating the clinical usefulness of prior testing of *HLA-A*31:01* genotype[7)].

3. 3 Phenytoin-related severe cutaneous adverse reactions

For phenytoin, an antiepileptic, a joint study was conducted among Taiwan, Malaysia, and Japan. It first demonstrated a significant association between the onset of SJS/TEN or DRESS/DIHS and *CYP2C9*3* (1075A>C, Ile359Leu), an activity-reducing polymorphism of *CYP2C9* which is a metabolizing enzyme for detoxification of phenytoin. A significant association was also demonstrated solely in Japanese SJS/TEN patients. It should be noted that the prevalence of *CYP2C9*3* in Japanese population is approximately 3%. Further, in a recent joint study among Taiwan, Thailand, and Japan, a significant association was observed between the onset of severe cutaneous adverse reaction related to phenytoin and *HLA-B*13:01, HLA-B*15:02, or HLA-B*51:01* in Taiwan. The prevalence of the 3 genotypes in the Japanese population was approximately 1.2%, 0.03%, 8.9%, respectively, and only *HLA-B*51:01* was found in 4 of the 9 Japanese SJS cases[8)]. Of note, the

number of Japanese cases was small and no significant differences were observed using Japanese cases alone. An association with *CYP2C9*3* polymorphism and *HLA-B*51:01* was also found in the analysis of drug eruption performed by Riken[9] albeit not limited to the severe reactions.

3. 4 Cold medicine (antipyretic and analgesic)-related SJS/TEN

An analysis of patients who developed SJS/TEN accompanied by severe ocular complications after use of cold medicines had found a significant association with *HLA-A*02:06* or *HLA-B*44:03*. The prevalence of *HLA-A*02:06* and *HLA-B*44:03* among Japanese is approximately 14% for both markers. And in patients under the same conditions, significant associations of SJS/TEN with 6 genetic polymorphisms, 3 types each on chromosome 15 and 16, were reported as a result of an genome-wide analysis performed by Associate professor Ueta from Kyoto Prefectural University of Medicine that employed an ethnicity-specific DNA array for Japanese (Japonica Array). To determine which one the association was attributable to, cold medicine-related SJS/TEN, SJS/TEN accompanied by a severe ocular involvements," or "cold medicine-related SJS/TEN accompanied by a severe ocular involvements, the NIHS analyzed 4 of the 6 genetic polymorphisms in patients administered antipyretics and analgesics which were the suspect drugs and found a significant association exclusively with "cold medicine-related SJS/TEN accompanied by a severe ocular involvements" in the 2 polymorphisms (rs6500265, rs9933632) of chromosome 16[11]. It should be noted that these 2 genetic polymorphisms exist in the area between the ZNF423 gene and the CNEP1R1 gene and consequently, another genetic polymorphism could be the causative with functional variation which is in linkage disequilibrium with these genetic polymorphisms.

3. 5 Sulfonamide-related severe cutaneous adverse reactions

In 8 SJS/TEN cases related to sulfonamides (sulfamethoxazole and salazosulfapyridine), a statistically significant higher prevalence of *HLA-A*11:01* was observed even after correction for multiple comparisons, when compared to that of healthy volunteers (in the Japanese population), [12]. This association was also found in an analysis of 7 Japanese DIHS cases. The prevalence of *HLA-A*11:01* in patients with severe cutaneous adverse reactions was 67% (10/15 cases) in total, a statistically significant higher prevalence compared to approximately 17% in the Japanese population (486/2 878 cases). On the other hand, the prevalence of Poor metabolizer based on the 3 types of defective alleles in N-acetyltransferase 2 (NAT2), a metabolizing enzyme for sulfonamide detoxification, did not significantly differ from the healthy Japanese volunteers, suggesting a possible involvement of sulfonamides, rather than the metabolite(s) in the onset. To explore this possibility, a computer docking simulation was carried out to analyze the interaction between sulfamethoxazole or salazosulfapyridine and *HLA-A*11:01* molecules. Both drugs were presumed to bind to *HLA-A*11:01* at the blood concentrations corresponding to their clinical doses. Therefore, it was considered that the 2 drugs and *HLA-A*11:01* molecules could directly interact with each other. As for salazosulfapyridine, a significant association with *HLA-B*13:01* for the onset of DRESS was reported[13] in Han Chinese. In our 15 severe cutaneous adverse reaction cases among Japanese, the HLA genotype was found in only 1 case of SJS related to sulfamethoxazole.

4. Closing remark

The above section provides an overview for the results of genomic analysis, etc. mainly with regards to SJS/TEN obtained by the NIHS. Some drugs have a limited number of cases, even though results have been published as research papers, and, many of the patients carrying genotypes associated with high risk do not develop the ADRs. Therefore, it is currently difficult in most cases to use these results immediately in clinical practice to avoid severe cutaneous adverse drug reactions 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 reactions (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.

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2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated March 31, 2020, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Pembrolizumab (genetical recombination)

Branded name (name of company)	Keytruda Injection 20 mg, 100 mg (MSD K.K.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Malignant melanoma Unresectable advanced or recurrent non-small cell lung cancer Relapsed or refractory classical Hodgkin lymphoma Unresectable urothelial carcinoma exhibiting progression after chemotherapy Advanced or recurrent, microsatellite instability-high (MSI-H) solid tumours exhibiting progression after chemotherapy (only when management cannot be achieved with standard therapies) Unresectable or metastatic renal cell carcinoma Recurrent or metastatic head and neck cancer

PRECAUTIONS (revised language is underlined)

[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	<u>Toxic epidermal necrolysis (TEN),</u> oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme
Reference information	Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 3-year period (February 2017 to January 2020) Cases involving toxic epidermal necrolysis: 7 (1 patient mortality) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 9 000 Japanese market launch: February 2017

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		No.	
1	Male 70s	Urothelial carcinoma (postoperative recurrentce) (bilateral metasitases to lung, metastases to right renal pelvis, type 2 diabetes mellitus, nephrogenic anaemia, cronic renal failure, end stage renal failure, renal disorder, hypertension, hypercholesterolaemia, hepatic steatosis, alcoholic hepatopathy, hyperuricaemia)	200 mg/ 3 courses in total, administered every 3 weeks ↓	**Toxic epidermal necrolysis, skin erosion, subcutaneous tissue ulcer, pruritic rash, erythema, erythema multiforme**	
				Day 1 of administration	The 1st couse of pembrolizumab was administered.
				1 day after start	Pyrexia, systemic pruritic rash developed.
				2 days after start	Rash, erythema developed. Back of head erosion emerged. Oral steroid was administered.
				14 days after start	Erythema multiforme developed. Betamethasone butylate propionate, levocetirizine hydrochloride 1 tablet (each) once/day started to treat systemic eczema (wheals like)
				21 days after start	The 2nd course of pembrolizumab was administered. Prednisolone 5 mg tablet once/day started for erhythema multiforme (until 45 days after the start)
				41 days after start (day of final administration)	The 3rd course of pembrolizumab was administered (final administration). Erythema multiforme remained. The patient was referred to the dermatology department and started to recieve fexofenadine hydrochloride 1 tablet once/day for systemic eczema and pruritis (until 68 days after the start).
				5 days after termination	Pyrexia developed. Systemic eczema intensified. A 10 cm painful back of head induration emerged. The patient was admitted to the hospital the next day on his own request. Prednisolone was increased to four 5 mg tablets 3 times (60 mg)/day (until 11 days after termination).
				8 days after termination	Betamethasone butylate propionate was administered for systemic eczema.
				12 days after termination	Prednisolone was reduced to two 5 mg tablets 3 times (30 mg)/day (until 14 days after termination)
				15 days after termination	Prednisolone was reduced to 1 tablet 3 times/day (until 17 days after termination)
				18 days after termination	Prednisolone was reduced to three 1 mg tablets 3 times 9 mg)/day (until 20 days after termination)
				21 days after termination	All subjective symptoms disappeared. Conditions of systemic eczema were improving (got crusted). Erythema multiforme remitted. Considering the disappearing tendency of systemic eczema, prednisolone was reduced to one 5 mg tablet once (5 mg)/day (until 22 days after termination).
				23 days after termination	Pyrexia developed. The patient had no subjective symptoms. Prednisolone was reduced to two 1 mg tablets once (2 mg)/day (until 32 days after termination).
				29 days after termination	The patient was discharged from the hospital on his request.

				31 days after termination	Erosion was formed and pyrexia at 38 °C and pain were recognized.
				33 days after termination	A slight tendency for reactivation was noted in the swelling of the lips. Rash was reactivated and prednisolone was increased to 1 tablet once/day (until 38 days after termination).
				36 days after termination	Systemic rash, erosion, effusion appeared (communicated from the patient who did not visit the hospital)
				39 days after termination (day of onset)	The patient was readmitted into the hospital. Methylprednisolone sodium succinate 1000 mg (steroid pulse) started. Systemic condition: pyrexia, general malaise, Site of skin condition: trunk, limb, lips Form of skin condition: exudadivum erythema, erosion, blisters, peeling Mucosal symptoms: pharyngodynia, lip erosion Particularly the chest, back, and buttock were entirely affected by erosion. Joint consultation with the dermatology dept. diagnosed the patient with toxic epidermal necrolysis (TEN) based on the erosion extended over 50% of the body surface that accompanied a SJS syndrome more advanced than a multiforme chronic purigo-like condition.
				40 days after termination	The patient was transferred to the HCU. Tachycardia was noted with a pulse rate 120/min. Chest Xp revealed no pleural effusion. Effusion was significant and intravalcular dehydration was noted. The patient received transfusion and steroid pulse but responded to neither of them. The patient was sedated with midazolam during the night.
				42 days after termination	The patient died. The cause of death was toxic epidermal necrolysis (TEN). No autopsy was performed.
	Concomitant drugs: Acetaminophen, alfacalcidol, amlodipine besilate, calcium polystyrene sulfonate, calcium preparation, sitagliptin phosphate hydrate, febuxostat, linagliptin, pioglitazone hydrochloride, allopurinol, candesartan cilexetil				

3
Revision of Precautions (No.312)

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 31, 2020.

1 Psychotropics
[1] Spiperone
[2] Timiperone
[3] Pipamperone hydrochloride

Branded name	[1] Spiropitan Tablets 0.25 mg, 1 mg (Sannova Co., Ltd.) [2] Tolopelon Tablets 0.5 mg, 1 mg, 3 mg, Tolopelon Fine Granules 1%, Tolopelon Injection 4 mg (Alfresa Pharma Corporation), and the others [3] Propitan Tablets 50 mg, Propitan Powder 10% (Sannova Co., Ltd.)
[Under Old instructions]	
Contraindications	Patients with Parkinson's disease or dementia with Lewy bodies

2 Psychotropics
[1] Sultopride hydrochloride
[2] Fluphenazine decanoate

Branded name	[1] Barnetil Tab. 50, 100, 200, Barnetil Fine Granule 50% (Kyowa Pharmaceutical Industry Co., Ltd.), and the others [2] Fludecasin Intramuscular Injection 25 mg (Mitsubishi Tanabe Pharma Corporation)
[Under Old instructions]	
Contraindications	Patients with Parkinson's disease or dementia with Lewy bodies
[Under New instructions]	
2. CONTRAINDICATIONS	Patients with Parkinson's disease or dementia with Lewy bodies

3 Psychotropics, peptic ulcer agents
Sulpiride

Branded name	Dogmatyl Tablets 50 mg, 100 mg, 200 mg, Dogmatyl Fine Granules 10%, 50%, Dogmatyl Capsules 50 mg, Dogmatyl Intramuscular Injection 50 mg, 100 mg (Astellas Pharma Inc.), and the others
[Under Old instructions]	
Careful Administration	Patients with Parkinson's disease or dementia with Lewy bodies
[Under New instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.**	Patients with Parkinson's disease or dementia with Lewy bodies

4 Psychotropics

Nemonapride

Branded name	Emilace Tablets 3 mg, 10 mg (LTL Pharma Co., Ltd.)
[Under Old instructions]	
Contraindications	Patients with Parkinson's disease or dementia with Lewy bodies
[Under New instructions]	
2. CONTRAINDICATIONS	Patients with Parkinson's disease or dementia with Lewy bodies

5 Psychotropics

[1] Haloperidol
[2] Haloperidol decanoate
[3] Bromperidol
[4] Mosapramine hydrochloride

Branded name	[1] Serenace Tablets 0.75 mg, 1 mg, 1.5 mg, 3 mg, Serenace Fine Granules 1%, Serenace Oral Solution 0.2%, Serenace Injection 5 mg (Sumitomo Dainippon Pharma Co., Ltd.), and others [2] Neoperidol injection 50, 100 (Johnson & Johnson K.K.) Halomonth Injection 50 mg, 100 mg (Janssen Pharmaceutical K.K.) [3] Impromen Tablets 1 mg, 3 mg, 6 mg, Impromen Fine Granules 1% (Janssen Pharmaceutical K.K.), and others [4] Cremin Tablets 10 mg, 25 mg, 50 mg, Cremin Granules 10% (Mitsubishi Tanabe Pharma Corporation)
[Under Old instructions]	
Contraindications	Patients with Parkinson's disease or dementia with Lewy bodies

6 Psychotropics

Pimozide

Branded name	Orap Tablets 1 mg, 3 mg, Orap Fine Granules 1% (Astellas Pharma Inc.)
[Under Old instructions]	
Contraindications (newly added)	Patients with Parkinson's disease or dementia with Lewy bodies

7 Psychotropics

[1] Blonanserin
[2] Perospirone hydrochloride hydrate

Branded name	[1] Lonasen Tablets 2 mg, 4 mg, 8 mg, Lonasen Powder 2%, Lonasen Tape 20 mg, 30 mg, 40 mg (Sumitomo Dainippon Pharma Co., Ltd.), and others [2] Lullan Tablets 4 mg, 8 mg, 16 mg (Sumitomo Dainippon Pharma Co., Ltd.), and others
[Under Old instructions]	
Careful Administration	Patients with Parkinson's disease or dementia with Lewy bodies
[Under New instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	Patients with Parkinson's disease or dementia with Lewy bodies
9.1 Patients with Complication or History of Diseases, etc.	

8 Autonomic nervous system agents

Aclatonium napadisilate

Branded name Abovis Capsule 25, 50 (FUJIFILM Toyama Chemical Co., Ltd.)

[Under Old instructions]

Contraindications Patients with Parkinson's disease or dementia with Lewy bodies

9 Blood and body fluid agents-miscellaneous

Pegfilgrastim (genetical recombination)

Branded name G-LASTA Subcutaneous Injection 3.6 mg (Kyowa Kirin Co., Ltd.)

[Under Old instructions]

Other Precautions (newly added) An increased risk of thrombocytopenia (a platelet count less than 5.0×10^4/μL) following administration of this drug has been reported in an epidemiological study conducted in Japan using a medical information database.

[Under New instructions]

15. OTHER PRECUTIONS
15.1 Information Based on Clinical Uses (newly added) An increased risk of thrombocytopenia (a platelet count less than 5.0×10^4/μL) following administration of this drug has been reported in an epidemiological study conducted in Japan using a medical information database.

*An investigation using MID-NET has been conducted (https://www.pmda.go.jp/files/000234445.pdf)

10 Antineoplastics-miscellaneous

Pembrolizumab (genetical recombination)

Branded name Keytruda Injection 20 mg, 100 mg (MSD K.K.)

[Under New instructions]

11. ADVERSE REACTIONS
11.1. Clinically Significant Adverse Reactions Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme

11 Antivirals

[1] Aciclovir (oral and injectable dosage forms)
[2] Valaciclovir hydrochloride

Branded name [1] Zovirax Tablets 200, 400, Zovirax Granules 40%, Zovirax for I.V. infusion 250 (GlaxoSmithKline K.K.), and others
[2] Valtrex Tablets 500, Valtrex Granules 50% (GlaxoSmithKline K.K.), and others

[Under Old instructions]

Adverse Reactions (Clinically Significant Adverse Reactions) Acute renal failure, tubulointerstitial nephritis

[Under New instructions]

11. ADVERSE REACTIONS
11.1. Clinically Significant Adverse Reactions Acute kidney injury, tubulointerstitial nephritis

12 Antivirals

Amenamevir

Branded name	Amenalief Tab. 200 mg (Maruho Co., Ltd.)
[Under Old instructions]	
Adverse Reactions (newly added)	**Erythema multiforme**: Erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuing this drug
[Under New instructions]	
11. ADVERSE REACTIONS (newly added)	Erythema multiforme

13 Antivirals

Baloxavir marboxil

Branded name	XofluzaTablets 10 mg, 20mg, Xofluza granule 2% portions (Shionogi & Co., Ltd.)
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Ischaemic colitis**: Ischaemic colitis may occur. If abnormalities such as abdominal pain, diarrhoea, and bloody stool are observed, appropriate measures should be taken.
[Under New instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Ischaemic colitis If abnormalities such as abdominal pain, diarrhoea, and bloody stool are observed, appropriate measures should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of 31 March, 2020)

◎: Products for which EPPV was initiated after March 1, 2020

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Mepolizumab (genetical recombination) Nucala for s.c. injection 100 mg	Glaxo Smith Kline K.K.	March 25, 2020
◎	Dupilumab (genetical recombination) *1 Dupixent 300 mg Syringe for S.C. Injection	Sanofi K.K.	March 25, 2020
	pH4-Treated normal human immunoglobulin*2 Privigen 10% I.V. Drip Infusion 5g/50mL, 10g/100mL, 20g/200mL	CSL Behring K.K.	February 21, 2020
	Entrectinib*3 Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	February 21, 2020
	Modafinil*4 Modiodal Tablets 100 mg	Alfresa Pharma Corporation	February 21, 2020
	Doravirine Pifeltro Tablets 100 mg	MSD K.K.	February 17, 2020
	Insulin aspart (genetical recombination) Fiasp Injection FlexTouch, Fiasp Injection Penfill, Fiasp Injection 100 U/mL	Novo Nordisk Pharma Ltd.	February 7, 2020
	Dolutegravir sodium/lamivudine Dovato combination tablets	Viiv Healthcare K.K.	January 31, 2020
	Freeze-dried recombinant herpes zoster vaccine (prepared from Chinese hamster ovary cells) Shingrix for intramuscular injection	Glaxo Smith Kline K.K.	January 29, 2020
	Turoctocog alfa pegol (genetical recombination) Esperoct for i.v. injection 500, 1000, 1500, 2000, 3000	Novo Nordisk Pharma Ltd.	January 29, 2020
	Perampanel hydrate*5 Fycompa tablets 2 mg, 4 mg	Eisai Co., Ltd.	January 23, 2020
	Lascufloxacin hydrochloride Lasvic Tablets 75 mg	Kyorin Pharmaceutical Co.,Ltd.	January 8, 2020
	Nintedanib ethanesulfonate*6	Boehringer Ingelheim	December 20,

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Ofev capsules 100 mg, 150 mg	Japan, Inc.	2019
Avelumab (genetical recombination)*7 Bavencio intravenous infusion 200 mg	Merck Biopharma Co., Ltd	December 20, 2019
Ceftolozane sulfate/tazobactam sodium*8 Zerbaxa Combination for Intravenous Drip Infusion	MSD K.K.	December 20, 2019
Certolizumab pegol (genetical recombination) *9 Cimzia 200 mg Syringe for S.C. Injection, Cimzia 200 mg AutoClicks for S.C. Injection	UCB Japan Co. Ltd.	December 20, 2019
Evocalcet*10 Orkedia Tablets 1 mg, 2 mg	Kyowa Kirin Co., Ltd.	December 20, 2019
Botulinum toxin type A Botox for injection 50 units, 100 units	Glaxo Smith Kline K.K.	December 20, 2019
Polyethylene glycol treated human normal immunoglobulin*11 Venoglobulin IH 5% I.V. 0.5 g/10 mL, 1g/20 mL, 2.5 g/50 mL, 5 g/100 mL, 10 g/200 mL, Venoglobulin IH 10% I.V. 0.5 g/5 mL, 2.5 g/25 mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	Japan Blood Products Organization	December 20, 2019
Freeze-dried sulfonated human normal immunoglobulin*12 Kenketsu Venilon- Ⅰ for Intravenous Injection 500 mg, 1000 mg, 2500 mg, 5000 mg	KM Biologics Co., Ltd.	December 20, 2019
Ropinirole hydrochloride Haruropi Tape 8 mg, 16 mg, 24 mg, 32 mg, 40 mg	Hisamitsu Pharmaceutical Co., Inc.	December 17, 2019
Omalizumab (genetical recombination) *13 Xolair for s.c. injection 75 mg, 150 mg, Xolair for s.c. injection syringe 75 mg, 150 mg	Novartis Pharma K.K.	December 11, 2019
Trafermin (genetical recombination) Retympa 250 μg Set for Otology	Nobelpharma Co., Ltd.	December 9, 2019
Burosumab (genetical recombination) Crysvita Subcutaneous Injection 10 mg, 20 mg, 30 mg	Kyowa Kirin Co., Ltd.	December 6, 2019
Lisdexamfetamine mesilate Vyvanse Capsules 20 mg, 30 mg	Shionogi & Co., Ltd.	December 3, 2019
Vortioxetine hydrobromide Trintellix Tablets 10 mg, 20 mg	Takeda Pharmaceutical Company Limited.	November 27, 2019
Necitumumab (genetical recombination) Portrazza Injection 800 mg	Nippon Kayaku Co., Ltd.	November 22, 2019
Ranibizumab (genetical recombination) *14 Lucentis solution for intravitreal injection 10mg/mL	Novartis Pharma K.K.	November 22, 2019
Ixekizumab (genetical recombination) *15 Taltz Subcutaneous Injection Syringes 80 mg, Taltz Subcutaneous Injection	Eli Lilly Japan K.K.	November 22, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
	Autoinjectors 80 mg		
	Venetoclax Venclexta Tablets 10 mg, 50 mg, 100 mg	AbbVie GK	November 22, 2019
	Safinamide mesilate Equfina Tablets 50 mg	Meiji Seika Pharma Co., Ltd.	November 20, 2019
	Roxadustat Evrenzo tablets 20 mg, 50 mg, 100 mg	Astellas Pharma Inc.	November 20, 2019
	Ivabradine hydrochloride Coralan Tablets 2.5 mg, 5 mg, 7.5 mg	Ono Pharmaceutical Co., Ltd.	November 19, 2019
	Quizartinib hydrochloride Vanflyta Tablets 17.7 mg, 26.5 mg	Daiichi Sankyo Co., Ltd.	October 10, 2019

*1 Chronic rhinosinusitis with nasal polyps (only in patients not adequately controlled with existing therapies)

*2 Agammaglobulinemia or hypogammaglobulinemia

*3 ROS1 fusion-positive, unresectable, advanced or metastatic non-small cell lung cancer

*4 Excessive daytime sleepiness associated with idiopathic hypersomnia

*5 Partial-onset seizures (including secondarily generalized seizures)

*6 Systemic sclerosis-associated interstitial lung disease

*7 Unresectable or metastatic renal cell carcinoma

*8 <applicable microorganisms> Zerbaxa-susceptible serratia bizio and haemophilus influenzae <applicable conditions> pneumonia and sepsis

*9 Plaque psoriasis, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma for which existing treatment methods are not sufficiently effective

*10 Hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism who are unable to undergo parathyroidectomy or relapse after parathyroidectomy

*11 Preoperative desensitization in renal transplantation with donor-specific antibodies

*12 Acute optic neuritis (when steroids are not sufficiently effective)

*13 Seasonal allergic rhinitis (only in severe to the most severe cases inadequately controlled with existing treatment)

*14 Retinopathy of prematurity

*15 Ankylosing spondylitis with inadequate response to existing therapies