Pharmaceuticals and Medical Devices Safety Information

No. 380 February 2021

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Available information is listed here

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

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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
BRAF	V-Raf murine sarcoma viral oncogene homolog B
CD4	Cluster of Differentiation 4
DNA	Deoxyribonucleic acid
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
HER	Human epidermal growth factor receptor
JC	John Cunningham
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PCR	Polymerase chain reaction
PML	Progressive Multifocal Leukoencephalopathy
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau

1

Revision of Precautions for Lidocaine Hydrochloride/Adrenaline Injections concerning Patients for Whom Anaesthesia Is Intended for Ears or Digits as Contraindication in Conduction or Infiltration Anaesthesia

1. Introduction

Lidocaine hydrochloride/adrenaline injections are used as local anaesthetics. The current package insert of lidocaine hydrochloride/adrenaline injections excluding preparations for dental use (hereinafter referred to as “this drug”) has so far specified “Patients for whom anaesthesia is intended for ears, digits, or penis [A necrotic condition may occur]” as a contraindication of this drug under the heading “Conduction/infiltration anaesthesia.”

Recently, based on the discussion at the 8th fiscal year (FY) 2020 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as the “Subcommittee on Drug Safety”) held on December 10, 2020, the package insert of this drug has been revised with respect to this contraindication. This section will introduce the details of the revision.

2. Background

“Patients for whom anaesthesia is intended for ears, digits, or penis” has so far been noted as a contraindication for this drug as mentioned above. Regarding the contraindication, the Oto-Rhino-Laryngological Society of Japan in January, the Japanese Society for Surgery of the Hand in February, and the Japanese Society for Surgery of the Foot in April 2020 submitted their own written requests asking that the package insert of this drug be revised to allow the use in conduction and infiltration anaesthesia in patients for whom anaesthesia is intended for ears, fingers, or digits, respectively. These written requests submitted from these academic societies presented the realities in clinical practice where adrenaline is used for the purpose of prolonging the duration of local anaesthesia and reducing bleeding in the operative field. The requests also stated that no literature published in Japan or overseas has been identified to report a necrotic condition following administration of this drug to ears and that a large scale study found no complications such as necrosis of fingers following administration of this drug, followed by their opinions that ears or digits should be excluded from the language “Patients for whom anaesthesia is intended for ears, digits, or penis”.

MHLW considered these requests from the academic societies and decided to discuss the revision of the contraindication.

3. Investigations by the Subcommittee on Drug Safety

(1) Excluding ears and digits from the current package insert language “Patients for whom anaesthesia is intended for ears, digits, or penis” as a contraindication

Related guidelines, Japanese and overseas standard textbooks, and published literature were reviewed for the discussion, and it was found that:

・Local anaesthetics containing adrenaline are recommended or noted as an anaesthetic approach for administration to ears or digits in the representative standard textbooks used in Japan and overseas as well as in the US guidelines.

・Regarding ears where blood flow is supplied by multiple vessels, occurrence of ischaemia following administration of this drug is unlikely.
・Regarding digits, there is a report that indicates recovery in blood flow after a certain period of time following administration without sequelae.

Taking into account these findings, the Subcommittee on Drug Safety decided that ears and digits may be excluded from the language for the contraindication “Patients for whom anaesthesia is intended for ears, digits, or penis.”

(2) Precaution in the Careful Administration section regarding patients for whom blood flow disorder and decreased blood flow are anticipated

It was decided that, as mentioned above, ears and digits may be excluded from the language “Patients for whom anaesthesia is intended for ears, digits, or penis” as contraindication. However, it was also decided that a precaution needs to be added to the Careful Administration section for patients for whom blood flow disorder and decreased blood flow are anticipated for the following reasons:

・A decrease in regional blood flow is anticipated from the pharmacological mechanism of adrenaline.
・Adverse reactions, although in a small number, have been reported in Japan.
・Cases of digital necrosis have also been reported in published literature.

(3) Package insert of adrenaline injections

Language “As an additive to local anaesthetics, this drug should not be used in ears, digits, or penis.” was included in the Precautions concerning Use section of the package insert of adrenaline injections indicated for prolongation of the action of local anaesthetics and prevention and treatment of intraoperative local haemorrhage.

In that respect, revision of the package insert for adrenaline injections was also considered necessary in line with the revision for this drug.

4. Closing remark

Healthcare professionals are requested to understand the gist of this revision, as well as to confirm the precautions in the package insert when considering use of lidocaine/adrenaline injections for conduction or infiltration anaesthesia, and determine whether to administer the drugs. Continued cooperation from healthcare professionals for the proper use of lidocaine/adrenaline injections would be appreciated.

[Reference]

・Materials 1-1 to 1-8 of the 8th FY 2020 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on December 10, 2020)
https://www.mhlw.go.jp/stf/newpage_15342.html (only in Japanese language)
・Revision of Precautions (PSEHB/PSD Notification No. 1221-2 dated December 21, 2020)
https://www.mhlw.go.jp/content/11120000/000707712.pdf (only in Japanese language)
English translation by PMDA
https://www.pmda.go.jp/files/000238105.pdf
https://www.pmda.go.jp/files/000238106.pdf

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated January 26, 2021, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Pomalidomide

Branded name (name of company)	Pomalyst Capsules 1 mg, 2 mg, 3 mg, 4 mg (Celgene K.K.)
Therapeutic category	Other antitumor agents
Indications	Relapsed or refractory multiple myeloma

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Adverse Reactions

Clinically Significant adverse Reactions

<u>Progressive multifocal leukoencephalopathy</u>

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 43-month period (April 2017 to October 2020)
Cases involving progressive multifocal leukoencephalopathy : 3 (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 4 200
Japanese market launch: May 2015

Case

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		No.
1	Male 50s	Multiple myeloma (diabetes mellitus)	4 mg 680 days (3-week administration, 1-week suspension)	**Progressive multifocal leukoencephalopathy (PML)**

Approx. 3 and a half years before administration	The patient developed multiple myeloma
Approx. 1 year and 3 months before administration	Administration of bortezomib, melphalan and dexamethasone was initiated.
Approx. 1 year before administration	Autologous haematopoietic stem cell transplantation was performed.
Approx. 6 months before administration	Administration of lenalidomide and dexamethasone was initiated.
Approx. 5 months before administration	The patient developed deep vein thrombosis. Administration of revlimid and dexamethasone was discontinued.
Day 1 of administration	Administration of pomalidomide in combination with dexamethasone was initiated.
Approx. 1 and a half years after administration (Date unknown)	The patient had difficulty speaking. Calculation mistakes occurred.
Approx. 1 year and 10 months after administration (Date unknown)	The patient had difficulty writing. Aphasia and left-right disorientation appeared.
680 days after administration (day of discontinuation)	Administration of pomalidomide and dexamethasone was discontinued.
21 days after discontinuation	The patient developed progressive multifocal leukoencephalopathy (PML).
22 days after discontinuation	Decreased density in the left parietal lobe identified in head MRI suggested the possibility of a tumor or brain abscess.
42 days after discontinuation	Histological and immunohistochemical exam detected histological findings of progressive multifocal leukoencephalopathy and JC virus antigens. PCR test of brain tissue detected JC virus DNA 2.6×10^4 copies/cell
Approx. 2 years after administration (Date unknown)	Decreased CD4 lymphocytes in peripheral blood were confirmed. (80/μL)
Date unknown	Mefloquine hydrochloride and mirtazapine were administered for the treatment of PML.
50 days after discontinuation	PML was not resolved.

Laboratory test values:

	42 days after discontinuation	Approx. 2 years after administration (Date unknown)
JC virus DNA (copies/cell)	2.6×10^4	-
CD4 lymphocytes（/μL）	-	80

Concomitant drugs: Dexamethasone

3
Revision of Precautions (No.320)

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 January 26, 2021.

1 Other antitumor agents
Alemtuzumab (genetical recombination)

Branded name	MabCampath 30 mg I.V. Infusion (Sanofi K.K.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Abnormal thyroid function may occur. Patients should be carefully monitored through thyroid function tests performed prior to, and during, administration of this drug.
11. ADVERSE REACTIONS	Immune disorder
11.1 Clinically Significant adverse Reactions	Immune disorder may occur such as autoimmune haemolytic anaemia, autoimmune thrombocytopenia, autoimmune hepatitis, aplastic anaemia, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuritis, post transfusion graft versus host disease, hypothyroidism, or hyperthyroidism, resulting in a fatal outcome reported in some cases. Administration of this drug should be discontinued if autoimmune haemolytic anaemia or autoimmune thrombocytopenia is observed.

2 Other antitumor agents
Pomalidomide

Branded name	Pomalyst Capsules 1 mg, 2 mg, 3 mg, 4 mg (Celgene K.K.)
[Under Old instructions]	
Adverse Reactions Clinically Significant adverse Reactions (newly added)	Progressive multifocal leukoencephalopathy (PML): Progressive multifocal leukoencephalopathy (PML) may occur. Patients should be carefully monitored during, and after, the treatment with this drug, and if symptoms such as disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia or quadriplegia), dyslalia, or speech loss are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, administration should be discontinued, and appropriate measures should be taken.
[Under New instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant adverse Reactions	Progressive multifocal leukoencephalopathy (PML) Patients should be carefully monitored during, and after, the treatment with this drug, and if symptoms such as disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia or quadriplegia), dyslalia, or speech loss are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, administration should be discontinued, and 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 January 2021)

◎: Products for which EPPV was initiated after January 1, 2021

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Rivaroxaban*1 Xarelto tablets 15 mg, 10 mg, Xarelto fine granules 15 mg, 10 mg, Xarelto OD tablets 15 mg, 10 mg	Bayer Yakuhin Ltd.	January 22, 2021
◎	Cetuximab sarotalocan sodium (genetical recombination) Akalux IV Infusion 250 mg	Rakuten Medical Japan K.K.	January 1, 2021
	Recombinant adsorbed quadrivalent human papillomavirus virus-like particle vaccine (yeast origin) *2 Gardasil Aqueous Suspension for Intramuscular Injection Syringes	MSD K.K.	December 25, 2020
	Baricitinib*3 Olumiant tablets 4 mg, 2 mg	Eli Lilly Japan K.K.	December 25, 2020
	Midazolam Buccolam Oromucosal Solution 2.5 mg, 5 mg, 7.5 mg, 10 mg	Takeda Pharmaceutical Company Limited.	December 10, 2020
	Enarodustat Enaroy tablets 2 mg, 4 mg	Japan Tabacco Inc.	December 8, 2020
	Incobotulinumtoxin A Xeomin 50 units for Intramuscular injection, Xeomin 100 units for Intramuscular injection, Xeomin 200 units for Intramuscular injection	Teijin Pharma Limited.	December 4, 2020
	Roxadustat*4 Evrenzo Tablets 20 mg, 50 mg, 100 mg	Astellas Pharma Inc.	November 27, 2020
	Dapagliflozin propylene glycolate hydrate*5 Forxiga 5 mg Tablets, Forxiga 10 mg Tablets	AstraZeneca K.K.	November 27, 2020
	Cabozantinib malate*6 Cabometyx tablets 20 mg, 60 mg	Takeda Pharmaceutical Company Limited.	November 27, 2020
	Binimetinib*7 Mektovi Tablets 15 mg	Ono Pharmaceutical Co., Ltd.	November 27, 2020

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Encorafenib*[7] Braftovi Capsules 50 mg, 75 mg	Ono Pharmaceutical Co., Ltd.	November 27, 2020
Brodalumab (genetical recombination) *[8] Lumicef Subcutaneous Injection 210 mg Syringe	Kyowa Kirin Co., Ltd.	November 27, 2020
Baloxavir marboxil*[9] Xofluza Tablets 20 mg, Xofluza Granules 2%	Shionogi & Co., Ltd.	November 27, 2020
Sofpironium bromide Ecclock gel 5%	Kaken Pharmaceutical Co., Ltd.	November 26, 2020
Niraparib tosilate hydrate Zejula capsules 100 mg	Takeda Pharmaceutical Company Limited.	November 20, 2020
Filgotinib maleate Jyseleca Tablets 100 mg, 200 mg	Gilead Sciences K.K.	November 18, 2020
Paliperidone palmitate*[10] Xeplion TRI Aqueous Suspension for IM Injection 175 mg, 263 mg, 350 mg, 525 mg	Janssen Pharmaceutical K.K.	November 18, 2020
Oxycodone hydrochloride hydrate*[11] OxyContin TR Tablets 5 mg, 10 mg, 20 mg, 40 mg	Shionogi Pharma Co., Ltd.	October 29, 2020
Glucagon Baqsimi Nasal Powder 3 mg	Eli Lilly Japan K.K.	October 2, 2020
Aripiprazole hydrate*[12] Abilify prolonged release aqueous suspension for IM injection 300 mg, 400 mg, Abilify prolonged release aqueous suspension for IM injection 300 mg syringe, Abilify prolonged release aqueous suspension for IM injection 400 mg syringe	Otsuka Pharmaceutical Co., Ltd.	September 25, 2020
Trastuzumab deruxtecan (genetical recombination) *[13] Enhertu For Intravenous Drip Infusion 100 mg	Daiichi Sankyo Co., Ltd.	September 25, 2020
Ravulizumab (genetical recombination) *[14] Ultomiris for Intravenous Infusion 300 mg	Alexion Pharma Godo Kaisha	September 25, 2020
Tildrakizumab (genetical recombination) Ilumya Subcutaneous Injection 100 mg Syringe	Sun Pharma Japan Limited	September 23, 2020
Siponimod fumaric acid Mayzent tablets 0.25 mg, 2 mg	Novartis Pharma K.K.	September 14, 2020
Ferric carboxymaltose Ferinject solution for injection/infusion 500 mg	Zeria Pharmaceutical Co., Ltd.	September 1, 2020
Isatuximab (genetical recombination) Sarclisa 100 mg I.V. Infusion, Sarclisa 500 mg I.V. Infusion	Sanofi K.K.	August 31, 2020
Indacaterol acetate/glycopyrronium bromide/ mometasone furoate Enerzair medium dose inhalation powder with hard capsules, Enerzair high dose	Novartis Pharma K.K.	August 26, 2020

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
inhalation powder with hard capsules		
Indacaterol acetate/mometasone furoate Atectura low dose inhalation powder with hard capsules, Atectura medium dose inhalation powder with hard capsules, Atectura high dose inhalation powder with hard capsules	Novartis Pharma K.K.	August 26, 2020
Sacubitril valsartan sodium hydrate Entresto Tablets 50 mg, 100 mg, 200 mg	Novartis Pharma K.K.	August 26, 2020
Capmatinib hydrochloride hydrate Tabrecta tablets 150 mg, 200 mg	Novartis Pharma K.K.	August 26, 2020
Satralizumab (genetical recombination) Enspryng Syringes for Subcutaneous Injection 120 mg	Chugai Pharmaceutical Co., Ltd.	August 26, 2020
Daprodustat Duvroq Tablets 1 mg, 2 mg, 4 mg, 6 mg	GlaxoSmithKline K.K.	August 26, 2020
Vadadustat Vafseo Tablets 150 mg, 300 mg	Mitsubishi Tanabe Pharma Corporation	August 26, 2020
Opicapone Ongentys Tablets 25 mg	Ono Pharmaceutical Co., Ltd.	August 26, 2020
Tirabrutinib hydrochloride*15 Velexbru Tablets 80 mg	Ono Pharmaceutical Co., Ltd.	August 21, 2020
Vonicog alfa (genetical recombination) Vonvendi Intravenous 1300	Shire Japan KK	August 17, 2020
Remimazolam besilate Anerem 50 mg for I.V. Injection	Mundipharma K.K.	August 7, 2020

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

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

*3 Atopic dermatitis with inadequate response to conventional treatments

*4 Nephrogenic anaemia

*5 Chronic heart failure (only in patients who are receiving standard of care)

*6 Unresectable hepatocellular carcinoma that has progressed after chemotherapy

*7 Unresectable advanced or recurrent BRAF-mutant colorectal cancer that has progressed after chemotherapy

*8 Ankylosing spondylitis and non-radiographic axial spondyloarthritis that respond inadequately to existing therapies

*9 Treatment and prevention of influenza virus infection types A and B

*10 Schizophrenia (only in patients who have been adequately treated with 4-week intramuscular paliperidone palmitate)

*11 Relief of moderate to severe chronic pain difficult to manage with non-opioid analgesics or other opioid analgesics

*12 Suppression of recurrence and relapse of mood episodes in bipolar I disorder

*13 HER2 positive unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy

*14 Atypical haemolytic uraemic syndrome

*15 Primary macroglobulinaemia and lymphoplasmacytic type lymphoma