

Pharmaceuticals and Medical Devices Safety Information

No. 357 October 2018

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

Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.



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Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency



Office of Safety I,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan E-mail: safety.info@pmda.go.jp

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Pharmaceuticals and Medical Devices Safety Information

No. 357 October 2018

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	Initiative of Revision of the Manuals for Management of Various Serious Adverse Drug Reactions (Part 2)		The Ministry of Health, Labour and Welfare (MHLW) prepared Manuals for Management of Various Serious Adverse Drug Reactions from fiscal year (FY) 2005 to 2010, and started to revise the manuals in FY 2016 based on the latest knowledge. In this issue, we will introduce the progress of revision in FY 2017.	4
2	Summary of the Relief System for Adverse Drug Reactions and Request for Cooperation with the System		Considering the low public awareness of the Relief System for Adverse Drug Reactions (ADRs) found in FY 2017, this section will introduce an overview of the System in order to ensure a widespread understanding.	8
3	Revision of Precautions (No. 297)	<i>P</i>	Amantadine hydrochloride (and 13 others)	22
4	List of Products Subject to Early Post-marketing Phase Vigilance		List of products subject to Early Post-marketing Phase Vigilance as of August 31, 2018.	29

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
ALP	Alkaline phosphatase
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
ANCA	Antineutrophil cytoplasmic antibody
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
BRCA	Breast cancer susceptibility gene
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HER	Human epidermal growth factor receptor
HPV	Human papilloma virus
HSD	Health Service Division
INR	International normalized ratio
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PT	Prothrombin time
SD	Safety Division
TEN	Toxic epidermal necrolysis
γ-GTP	Gamma-glutamyl transpeptidase

Initiative of Revision of the Manuals for Management of Various Serious Adverse Drug Reactions (Part 2)

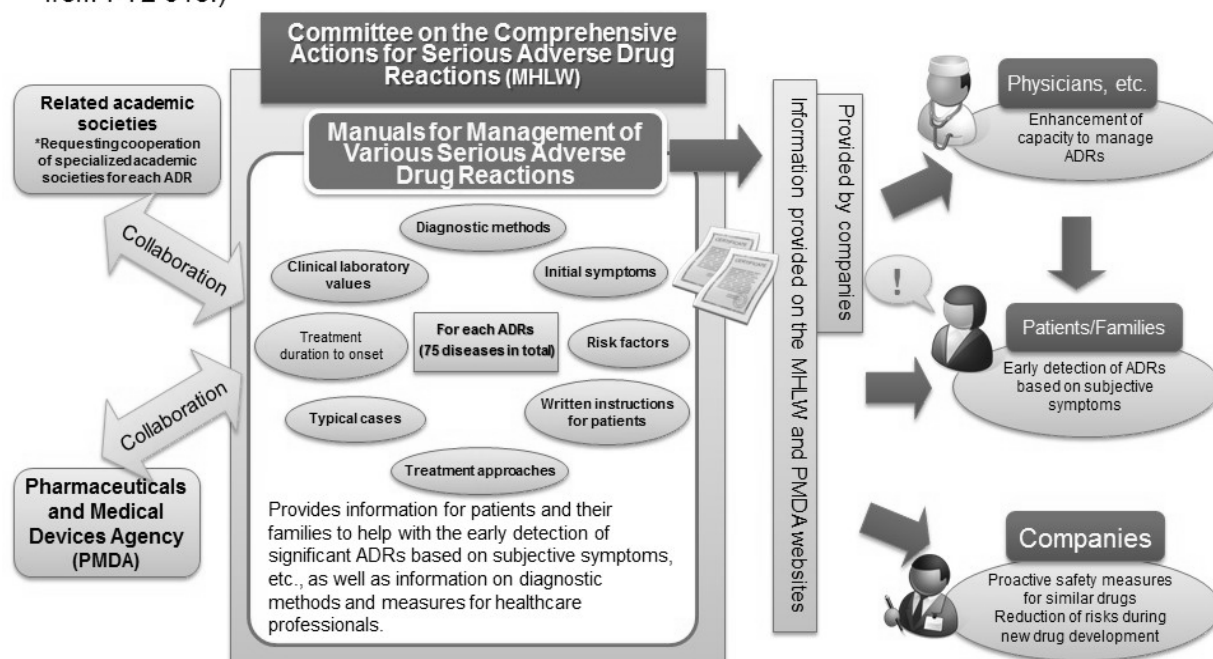
1. Revision of the Manuals for Management of Various Serious Adverse Drug Reactions

The Manuals for Management of Various Serious Adverse Drug Reactions were compiled from FY 2005 to FY 2010 by the committee on the comprehensive actions for serious adverse drug reactions who reviewed and compiled the drafts prepared by manual preparation committees organized in related academic societies through discussion with the Japanese Society of Hospital Pharmacists (JSHP) as entrusted by the MHLW. The drafts were prepared with reference to academic papers, various guidelines, health and labour sciences research project reports, PMDA health and welfare service reports, etc. At present, the manuals are available for a total of 75 diseases.

Since FY 2016, we have been working on the revision of the manuals based on the latest knowledgeⁱ.

Revision of the Manuals for the Management of Various Serious Adverse Drug Reactions

The Manuals for the Management of Various Serious Adverse Drug Reactions prepared between FY 2005 and 2010 (a total of 75 diseases) will be revised/updated based on the recent knowledge to contribute to early detection and early management of adverse drug reactions (ADRs) in clinical settings, etc. (Manuals will be prioritized for review through a 5-year period from FY2 016.)



ⁱ Pharmaceuticals and Medical Devices Safety Information No.348 (<http://www.pmda.go.jp/files/000221054.pdf>)

2. Progress of Revision

In FY 2017, we worked on the revision of the following manuals. These revised versions were compiled through discussions at the meeting of the Committee on the Comprehensive Actions for Serious Adverse Drug Reactions held on May 31, 2018 and published in June 2018.

Manuals newly prepared or revised in FY 2017

Author	Manual title	Category
The Japanese Dermatological Association	Erythema multiforme	New
Japanese Society of Nephrology	Acute kidney injury (acute tubular necrosis)	Revision
	Interstitial nephritis (tubulointerstitial nephritis)	Revision
	Nephrotic syndrome	Revision
	Renal disorder due to vasculitis (including ANCA-associated vasculitis)	Revision
	Nephrogenic diabetes insipidus	Revision
	Tumor lysis syndrome	Revision
	Hypokalemia	New
The Japan Diabetes Society	Hyperglycemia	Revision
	Hypoglycemia	Revision
Japanese Society of Oral and Maxillofacial Surgeons	Antiresorptive agents-related osteonecrosis/osteomyelitis of jaw	Revision
The Japanese Orthopaedic Association	Osteoporosis	Revision

An outline of revisions in each field is provided below:

(1) Dermatology

In the field of dermatology, a new manual for “Erythema multiforme” was prepared. Unlike Stevens-Johnson syndrome, which is a severe drug eruption, erythema multiforme does not require potent treatment such as large dose steroid therapy or large-dose immunoglobulin therapy. However, major erythema multiforme which is accompanied by pyrexia and/or enanthema needs to be differentiated from Stevens-Johnson syndrome. The manual describes the required differentiation from clinical and histopathological perspectives.

The existing manual of Stevens-Johnson syndrome describes the differences of the syndrome from erythema multiforme in terms of skin histopathology but does not include details or histological images of the clinical presentation of erythema multiforme. The treatment for erythema multiforme is not described in the existing manual either. In response to that, a new manual dedicated to erythema multiforme was prepared this time.

(2) Nephrology

In the field of nephrology, the entire field was reviewed and the existing manuals were reorganized into 7 manuals, namely, “Acute kidney injury (acute tubular necrosis),” “Interstitial nephritis (tubulointerstitial nephritis),” “Nephrotic syndrome,” “Renal disorder due to vasculitis (including ANCA-associated vasculitis),” “Nephrogenic diabetes insipidus,” “Tumor lysis syndrome” and “Hypokalemia.” The contents were also revised based on, among other things, the Treatment Guidelines for Drug-induced Kidney Injury (2016) of the Japanese Society of Nephrology and in accordance with the adoption of “acute kidney injury (AKI)” as an internationally recognized disease name/concept instead of “acute renal failure,” which had previously been used.

While various drug-induced electrolyte abnormalities occur in the treatment of renal diseases, hypokalemia is likely to be overlooked and may accelerate kidney injury once it becomes chronic. Thus, a manual for hypokalemia was newly prepared to call attention.

(3) Metabolism and endocrinology

In the field of metabolism and endocrinology, manuals for “Hyperglycemia” and “Hypoglycemia” were revised.

For hyperglycemia, revisions were made mainly to call attention to the use of recently launched immune checkpoint inhibitors, because fulminant type 1 diabetes mellitus, though very rare, may occur following their use. Thus, related descriptions and cases of fulminant type 1 diabetes mellitus induced by these drugs were added to the manual.

For hypoglycemia, revisions were made in accordance with a nationwide survey related to the background of severe hypoglycemia, which was conducted by the Japan Diabetes Society. This survey revealed that significant risk factors for the occurrence of severe hypoglycemia include advanced age, achievement of strict glycemic control, and use of sulphonylureas (SU). These findings are reflected in the revision.

In addition, given that the occurrence of hyperglycemia and hypoglycemia is more common in elderly people, a revision was also made to include a message to communicate the risk and relevant information to patients’ families or caregivers as well as patients themselves in the “For patients” section in both manuals.

(4) Oral cavity

In the field of oral cavity, the previous version titled “Bisphosphonate-related osteonecrosis of Jaw,” was revised as “Antiresorptive agents-related osteonecrosis/osteomyelitis of jaw” and the revised version reflects the development of non-bisphosphonates bone resorption inhibitors and associated revision of the position paper by the Japanese Society of Oral and Maxillofacial Surgeons in 2016.

The contents were updated and improved to clarify that dental treatment excluding tooth extraction is not regarded as a particular risk factor while invasive dental treatment involving bone had previously been considered as the greatest risk factor, to include recent findings such as the importance of cumulative doses, and to add photos related to symptoms.

(5) Bone

In the field of bone, revisions were made to “Osteoporosis.” The first version prepared in May 2009 focused on oral steroids as causative agents of adverse drug reactions. The revisions made this time are in accordance with subsequent publication overseas of guidelines and position statements concerning bone loss in association with the use of aromatase inhibitors and androgen deprivation therapy as the treatment for sex hormone depletion.

In addition, the descriptions of treatment approaches were updated in accordance with the revision of the Guidelines on the Management and Treatment of Steroid-induced Osteoporosis by the Japanese Society for Bone and Mineral Research in 2014, and the latest knowledge was also incorporated.

(6) Others (Items common to all fields)

Along with the revisions to the manuals, descriptions related to the Relief System for Adverse Drug Reactions were also added. Explanations about relief for sufferers of adverse drug reactions were added at the end of the section “About this manual” at the beginning of each manual, and the manuals also provide the number of relief benefits in the past 5 years under the Relief System for Adverse Drug Reactions as Annex 3 and information concerning the Relief System for Adverse Drug Reactions as Annex 4 at the end of each manual.

3. Closing Comments

We continue to revise manuals in FY 2018. Please also make good use of the manuals listed on the websites of MHLW and PMDAⁱⁱ.

ⁱⁱ MHLW website “Manuals for Management of Various Serious ADRs” (for healthcare professionals)
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryuu/iyakuhin/topics/tp061122-1.html (only in Japanese)
PMDA website “Manuals for Management of Various Serious ADRs” (for healthcare professionals)
<http://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html> (only in Japanese)

2

Summary of the Relief System for Adverse Drug Reactions and Request for Cooperation with the System

1. Introduction

The Relief System for Adverse Drug Reactions (ADRs) (hereinafter referred to as “the Relief System”) was established in 1980 to bring prompt relief to people who suffer from adverse health effects such as disorders or disabilities caused by adverse reactions to pharmaceuticals despite using such products properly. This is a public service funded by contributions from marketing authorization holders (MAHs) of pharmaceuticals etc. as a way to fulfill some of their social responsibilities.

A similar system for biological products, the Infections derived from Biological Products Relief System, was established in 2004 to bring prompt relief to people who suffered from adverse health effects such as disorders or disabilities caused by viral infections, etc. acquired through the use of biological products despite their proper use. Furthermore, adverse reactions to regenerative medical products and infections, etc. acquired through the use of such products is now being covered by the Relief System since November 25, 2014.

In this Relief System, a total of 21 507 cases have been granted relief benefits since the establishment of the Relief System in 1980 until the end of fiscal year (FY) 2017.

In this Relief System, a total of 21 507 cases have been granted relief benefits since the establishment of the Relief System in 1980 until the end of fiscal year (FY) 2017.

2. Awareness of the Relief System for Adverse Drug Reactions ^{Note 1)}

Awareness of the Relief System among the general public in FY2017 was 32.6% in total:

the 10.3% who answered that they “were aware” of the Relief System and 22.3% who answered that they “have heard about” the Relief System. It is inferred that some people may not file an application for compensation for adverse health effects associated with ADRs that they have suffered because they are unaware of the Relief System.

On the other hand, the awareness among healthcare professionals was 84.5% in total: the 62.3% who answered that they “were aware” of the Relief System and the 22.2% who answered that they “have heard about” the Relief System. By occupational category, awareness was 93.5% among physicians, 98.3% among pharmacists, 62.5% among nurses, and 83.0% among dentists. Among the healthcare professionals who were aware of the Relief System, the proportion of them who had been involved in a filing procedure was 9.4% in total: 10.2% among physicians, 12.6% among pharmacists, 6.0% among nurses, and 5.4% among dentists. Furthermore, in all application forms related to relief benefits, the field for “the source of information related to the Relief System” (select from “Physician,” “Dentist,” “Pharmacist,” “Other medical facility staff,” “Newspaper/TV, etc.” and “Others”) was included in April 2016 to grasp the sources of information related to the Relief System. The 2017 results showed “Physician” in 512 answers (34.0%), “Others” (the Internet) in 220 answers (14.6%), “Newspaper/TV etc.” in 171 answers (11.4%) and “Pharmacist” in 136 answers (9.0%) in descending order (multiple answers acceptable)^{Note 2)}.

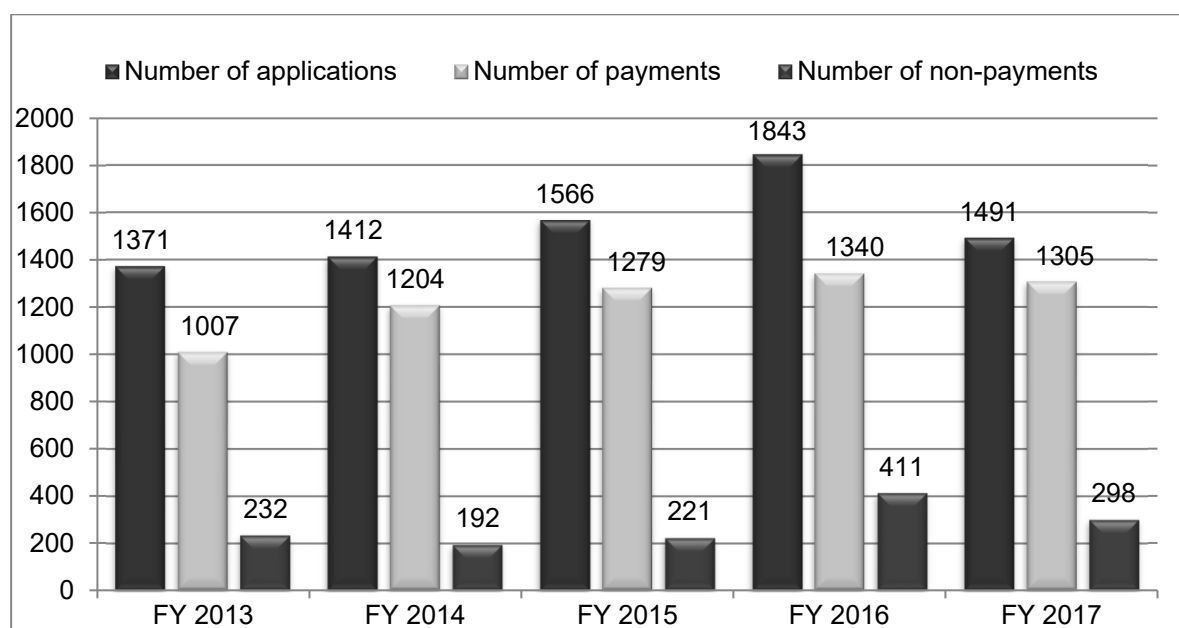
Healthcare professionals should provide information on the Relief System to people who have suffered from adverse health effects associated with adverse reactions to drugs or regenerative medical products so that they can utilize the Relief System, and should also cooperate with the preparation of medical certificates, etc. when people suffering from adverse health effects file an application for compensation.

3. Status of payment/non-payment cases in the Relief System

The annual numbers of applications and payments in the Relief System between FY 2013 and FY 2017 are shown in Figure 1. In 2017, the number of applications was 1 491, the number of payments was 1 305, and the number of non-payments was 298. Details of reasons for non-payments are shown in Figure 2.

In addition, the goal of standard administrative processing time ^{Note 3)} from when PMDA receives an application to when PMDA notifies the applicant of the decision was within 6 months in 60% or more of cases for which payment or non-payment was determined. The actual achievement percentage in FY2017 was 69.3%.

Figure 1. Number of payments and non-payments under the Relief System for Adverse Drug Reactions (FY2013 to FY2017)



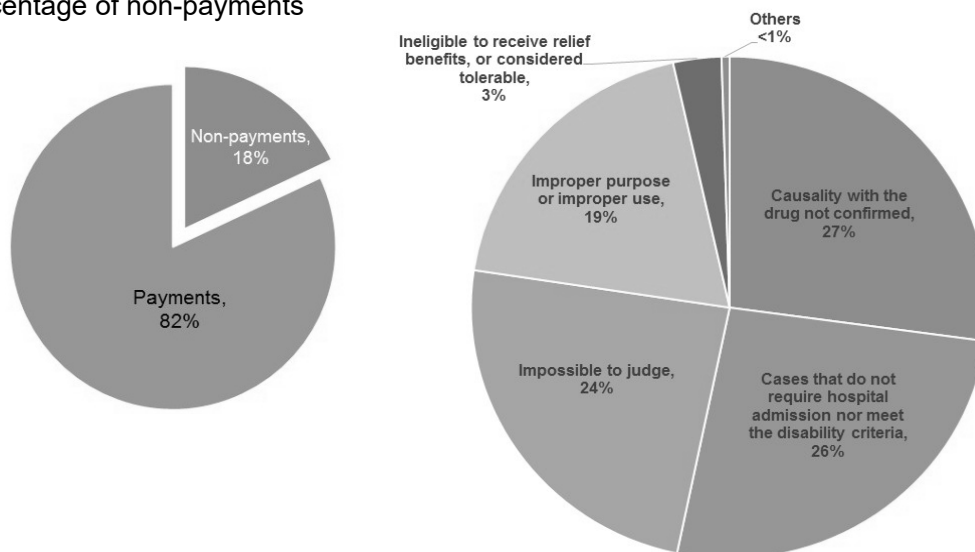
(Explanation of the figure)

* The number of cases is based on the number of applicants. Therefore, if the same applicant submits a claim for the same cause after a first claim for it has been submitted, it is counted as 1 case.

* The number of applications and total number of payments and non-payments made within the FY are not consistent since a certain period is required from receipt of the application to the decision on benefit payments.

Figure 2. Reasons for non-payments between FY2013 and FY2017

Percentage of non-payments



4. Adverse health effects subject to the Relief System

Adverse health effects subject to the Relief System include disorders (severe enough to require hospital admission), disabilities (serious enough to significantly limit daily life activities), and deaths despite the proper use of pharmaceuticals or regenerative medical products (hereinafter referred to as “drugs”).

Drugs subject to the Relief System include those prescribed or used at hospitals and clinics as well as those purchased at pharmacies, etc.; however, some drugs such as anticancer drugs and immunosuppressants are excluded from this Relief System. In addition, claims for medical expenses for disorders, etc. have a deadline, and claims for subjected payments of medical expenses must be submitted within 5 years after such expenses have been paid.

Please refer to the details of the Relief System noted on the PMDA website (<https://www.pmda.go.jp/relief-services/outline/0001.html>).

[Types and amounts of relief benefits (as of April 01, 2018)]

Medical Expenses (costs borne by the patients, not including health insurance payments)

- Actual costs of treatment for disease caused by ADRs will be compensated.

Medical Allowance (34 400 to 36 400 yen per month)

- Benefits are provided for other costs than medical costs for treatment of diseases caused by ADRs.

Disability Pension (Grade 1: 2 767 200 yen per year, Grade 2: 2 214 000 yen per year)

- Benefits are provided to compensate for living costs, etc., of patients aged 18 years or older, who suffer from a certain degree of disability caused by ADRs, etc.

Pension for Raising Children with disabilities (Grade 1: 865 200 yen per year, Grade 2: 692 400 yen per year)

- Benefits are provided to people who are responsible for raising children under 18 years who suffer from a certain degree of disability caused by ADRs

Bereaved Family Pension (2 420 400 yen)

- Benefits are provided for bereaved families to rebuild their lives following the deaths of their main providers from ADRs, etc.

Lump-Sum Benefits for Bereaved Family (7 261 200 yen)

- Benefits are provided to bereaved families for condolence and sympathy following death due to ADRs, etc. of a family member who is not the main provider.

Funeral Expenses (206 000 yen)

- Benefits are provided for the costs of holding a funeral for people who died of ADRs.

[Cases of relief benefit payments]

<Case 1> A case of deep vein thrombosis caused by a drug for the treatment of dysmenorrhea, for which medical expenses and medical allowance benefits were provided

A woman in her 20s developed pulmonary thromboembolism and deep vein thrombosis after using Yaz Combination Tablets (drospirenone/ethinylestradiol betadex) and received inpatient treatment. Medical expenses and medical allowance benefits were provided.

<Case 2> A case of anaphylactic shock caused by x-ray contrast medium, for which medical expenses, medical allowance, lump-sum benefits for bereaved family, and funeral expenses benefits were provided

A man in his 50s experienced anaphylactic shock after using Iopamiron Injection (iopamidol) and died. Medical expenses, medical allowance, lump-sum benefits for bereaved family, and funeral expenses benefits were provided.

<Case 3> A case of drug-induced hypersensitivity syndrome caused by an antispasmodic agent, for which medical expenses, medical allowance, and disability pension benefits were provided

A man in his 50s experienced drug-induced hypersensitivity syndrome (DIHS) after using Trancolon Combination Tablets (mepenzolate bromide/phenobarbital), resulting in respiratory dysfunction due to secondary obliterative bronchiolitis. Medical expenses, medical allowance, and disability pension benefits were provided.

<Case 4> A case of toxic epidermal necrolysis caused by an OTC drug, for which medical expenses and medical allowance benefits were provided

A man in his 30s experienced toxic epidermal necrolysis (Lyell's syndrome) after using Bufferin A and received inpatient treatment. Medical expenses and medical allowance were provided.

5. Cases in which the proper use of pharmaceuticals could not be confirmed

Of the 1 354 non-payment cases from FY2013 to FY2017^{Note 4)}, the reason for nonpayment in approximately one-fifth of them was that the proper purpose or method of use of the pharmaceutical could not be confirmed (Figure 2). The most recent (approximately the last year) reasons why the method of use was not considered proper are presented in this section together with the description provided in the package inserts or specific cases. Table 1 shows the most common pharmaceuticals for which the method of use was not considered proper.

Table 1. Number of cases in which the method of use of the pharmaceutical was not considered proper (FY2013 to FY2017)

Name of causative drug	FY2013	FY2014	FY2015	FY2016	FY2017	Total (cases)
Lamotrigine	26	24	23	24	9	106
Thiamazole	1	2	5	3	1	12
Lithium carbonate	3	0	1	8	0	12
Others	43	29	25	19	18	134
Total (cases)	73	55	54	54	28	264

(1) Cases in which pharmaceuticals were used in ways other than the approved dosage and administration

Lamotrigine (Lamictal Tablets) was involved in many of the cases in which pharmaceuticals were used in ways other than the approved dosage and administration.

Healthcare professionals should confirm the package insert once again and pay attention to the dosage and administration when using pharmaceuticals.

<Case> A case of drug-induced hypersensitivity syndrome caused by lamotrigine

A teenage woman prescribed Lamictal Tablets for epilepsy in combination with sodium valproate started the treatment at 50 mg every day. This was not accepted as proper use.

Improper use of lamotrigine

The incidence of skin disorders increases when lamotrigine is administered at higher doses or frequencies than the approved ones. Healthcare professionals have repeatedly been urged to adhere to the approved dosage and administration, including the dosage when initiating administration and the dosage when titrating, as well as alternate-day administration and the timing of titration, through various means including the distribution of a Dear Healthcare Professional Letter of Rapid Safety Communication (Blue Letter) in February 2015.

Despite such precautions, there has been no end to cases of patients who file an application for compensation for ADRs but fail to receive the relief benefit payments because they are not accepted as proper use.

Many of these cases in which payment was not approved due to improper use included the prescription of excessive dosages at the start of administration or during titration up to the maintenance dose, or an earlier dose increase.

Dosage and administration of lamotrigine are closely regulated in terms of dosage and dose increase intervals depending on the specific indications and concomitant pharmaceuticals. Please make sure to read the package insert carefully before use.

Dosage and administration when used in epileptic patients (adults) is shown below as an example. Please refer to the package insert of lamotrigine for other examples of closely regulated dosage and administration.

Use in epileptic patients: Adults – from the package insert for Lamictal Tablets that was revised in March 2017

Figure 3. Examples of concomitant medications with lamotrigine

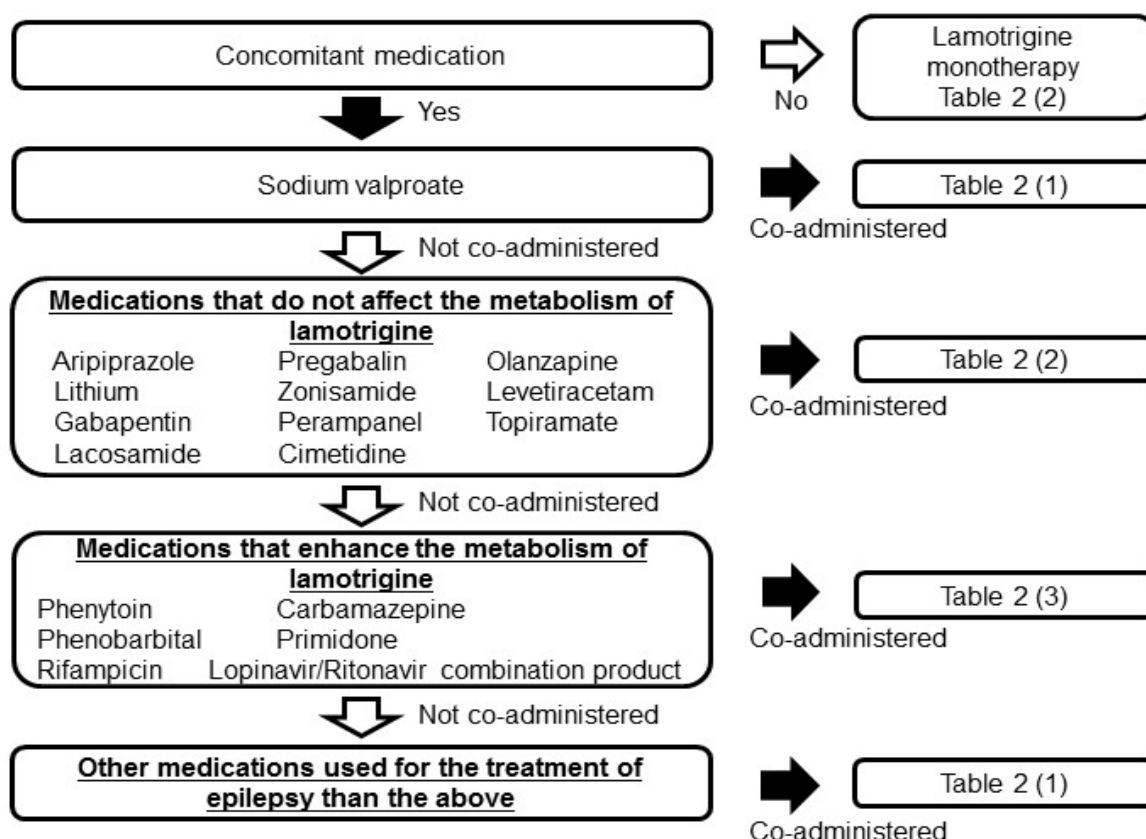


Table 2. Dose of lamotrigine at the start of administration

	Week 1/2	Week 3/4	From Week 5		Maintenance phase
(1)	25 mg once every 2 days	25 mg/day	Gradual dose increase by 25 to 50 mg/day every 1 to 2 weeks		100 to 200 mg/day

	Week 1/2	Week 3/4	Week 5	From Week 6	Maintenance phase
(2)	25 mg/day	50 mg/day	100 mg/day	Gradual dose increase by 100 mg/day every 1 to 2 weeks	100 to 200 mg/day

	Week 1/2	Week 3/4	From Week 5		Maintenance phase
(3)	50 mg/day	100 mg/day	Gradual dose increase by 100 mg/day every 1 to 2 weeks		200 to 400 mg/day

(2) Cases in which the required tests are not performed

If the package inserts specify that certain tests must be conducted for use of pharmaceuticals and these tests are not conducted, the method of use will not be considered proper.

To detect ADRs early and prevent them from becoming serious, it is considered necessary to perform appropriate tests and provide explanations about the necessity of tests in a way that patients can understand. Thus, healthcare professionals are strongly advised to read through the package insert once again.

<Case 1> A case of pancytopenia caused by ticlopidine hydrochloride

A man in his 80s did not undergo any blood tests over a period of 35 days from the start of treatment with ticlopidine hydrochloride until confirmation of persisting pyrexia and pancytopenia. The case was thus not approved as proper use.

Description in the package insert of ticlopidine hydrochloride (partial excerpts)

[WARNINGS]

Ticlopidine hydrochloride has been reported to be associated with clinically significant adverse reactions such as thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder, which usually occur within 2 months of initiation of treatment, resulting in a fatal outcome in some cases. [See “Clinically Significant Adverse Reactions”.]

Patients treated with this drug should be closely monitored particularly for initial symptoms of the above adverse reactions for the first 2 months of treatment, and should undergo blood cell counts (including differential leukocyte count) and liver function tests at 2-week intervals, in principle. If any evidence of the above adverse reactions is seen, administration of this drug should be discontinued immediately, and appropriate measures should be taken. Caution and close monitoring of the above adverse reactions should be exercised with routine blood testing during treatment with this drug.

[Clinically Significant Adverse Reactions]

Agranulocytosis (initial symptoms: fever, sore throat, malaise, etc.)

Agranulocytosis may occur (particularly within 2 months of initiation of treatment). Patients treated with this drug should be closely monitored, and if any of the initial symptoms are observed, administration of this drug should be discontinued immediately, and appropriate measures including blood testing (blood cell count etc.) should be taken.

<Case 2> A case of drug-induced liver injury caused by fenofibrate

A man in his 30s did not undergo any liver function tests over a period of 56 days from the start of treatment with Lipidil Tablets (fenofibrate) until confirmation of hepatic function disorder. Thus, the case was not approved as proper use.

Description in the package insert of Lipidil Tablets (partial excerpts)

[CONTRAINDICATIONS]

Patients with liver disorder [This drug may exacerbate liver disorder.]

[Important Precautions]

Increases in AST (GOT), ALT (GPT), γ -GTP, LDH, and ALP, jaundice, and hepatitis may occur. Liver function tests should be performed once a month for the first 3 months of treatment and every 3 months thereafter.

[Clinically Significant Adverse Reactions]

Liver disorder (0.1–<5%): Hepatitis, jaundice, and liver function disorder associated with significant increases in AST (GOT), ALT (GPT), etc. may occur. Patients treated with this drug should be closely monitored with routine liver function tests, and if any abnormal findings are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

(3) Cases in which pharmaceuticals were used in patients who met CONTRAINDICATIONS or RELATIVE CONTRAINDICATIONS

In some cases, pharmaceuticals were used in patients despite the fact that they met CONTRAINDICATIONS or RELATIVE CONTRAINDICATIONS and the use was not considered proper.

Healthcare professionals are strongly advised to use pharmaceuticals properly fully taking into account the patient's underlying disease/complications, history of allergies, history of ADRs, medication history at other hospitals, etc.

<Case 1> A case of co-administration of miconazole gel with warfarin

A man in his 80s who was on continuous treatment with Warfarin Tablets received Florid Oral Gel (miconazole gel) in combination and experienced markedly increased PT-INR, coagulopathy, and cerebral hemorrhage. Since the combination use of these drugs is contraindicated, the case was not approved as proper use.

Description in the package insert of miconazole gel (partial excerpts)

[CONTRAINDICATIONS]

Patients receiving treatment with warfarin potassium, pimozide, quinidine, triazolam, simvastatin, azelnidipine, nisoldipine, blonanserin, ergotamine tartrate, dihydroergotamine mesylate, rivaroxaban, asunaprevir, and lomitapide mesylate (see "Interactions").

[Contraindications for co-administration]

Drug name etc.

Warfarin potassium

Warfarin

Signs, Symptoms, and Treatment

The effect of warfarin may be intensified, or serious hemorrhage or significant increase in international normalized ratio (INR) may occur. It has also been reported that the effect of warfarin even persisted long after discontinuation of co-administration, which led to serious hemorrhage. Treatment with warfarin should be prioritized over this drug and this drug should not be used in patients who require treatment with warfarin.

Mechanism/Risk Factors

Interactions with these drugs may possibly occur because miconazole inhibits cytochrome P450 enzymes, which are involved in the metabolism of warfarin.

<Case 2> A case of acute aggravation of chronic renal failure caused by arbekacin sulfate

A man in his 80s received arbekacin sulfate injection 200 mg daily despite the fact that he was at an advanced age and had decreased renal function associated with diabetic nephropathy, and he experienced acute aggravation of chronic renal failure. The case was thus not approved as proper use.

Description in the package insert of Arbekacin Sulfate Injection (partial excerpts)

[RELATIVE CONTRAINDICATIONS]

Patients with renal disorder (High blood concentrations may persist long, which can exacerbate renal disorder. Severe adverse reactions such as eighth cranial nerve disorder may also occur. [See "PHARMACOKINETICS"].)

[DOSAGE AND ADMINISTRATION]

Treatment in adults

The usual adult dosage is 150 to 200 mg (potency) of arbekacin sulfate once daily administered by intravenous infusion over a period of 30 minutes to 2 hours. The daily dose of 150 to 200 mg (potency) may be divided into two doses, if necessary, which are administered by intravenous infusion. If intravenous therapy is difficult, arbekacin sulfate may be injected intramuscularly at a daily dose of 150 to 200 mg (potency) in a single dose or two divided doses. The dosage should be adjusted according to age, body weight, and symptoms.

[Important Precautions]

Serious renal disorder, such as acute renal failure, may occur. Patients treated with this drug should be closely monitored with renal function tests etc. during treatment. The drug should be carefully administered, particularly to elderly patients and patients with serious underlying disease and/or concurrent disease, with close monitoring of their condition and due caution when selecting the dose etc.

(4) Cases in which patients used pharmaceuticals by their own judgment without the directions of a physician

When a patient uses a pharmaceutical that should be used as prescribed by a physician by the patient's own judgment without following a physician's instructions, or uses a pharmaceutical that has been prescribed for a family member or friend of the patient, the purpose and the method of use will not be approved as proper.

Healthcare professionals are strongly advised to provide accurate guidance on the days of administration or the medication requirements and dosage, etc. by giving specific instructions verbally, etc. so that patients will be able to use the pharmaceuticals properly.

<Case> A case of oculomucocutaneous syndrome caused by garenoxacin mesilate hydrate

A man in his 30s had symptoms of the common cold, etc. and used the remaining Geninax Tablets (garenoxacin mesilate hydrate) that had previously been prescribed by a physician on his own judgment. The case was thus not approved as proper use.

(5) Other cases in which pharmaceuticals were used in other ways than described in the package insert

With regard to the use of pharmaceuticals for any other purposes than the indications provided in the package insert, the method of use of pharmaceuticals was not approved as proper in cases in which the tests/diagnostic criteria, etc. that are necessary for the selection of patients or appropriate dosage and administration, etc. had not been clarified and the safety of the use had not been secured; cases in which precautions for use had been given but were not followed in relation to the selection of patients; and cases in which pharmaceuticals were continuously used despite precautions concerning discontinuation of use.

Healthcare professionals are strongly advised to read through the related package insert once again.

<Case 1> A case of erythema multiforme caused by Vonosap Pack

A man in his 50s was diagnosed with *Helicobacter pylori* gastritis without performing endoscopy, and Vonosap Pack was used. The case was thus not approved as proper use.

Description in the package insert of VONOSAP Pack (partial excerpts)

[INDICATIONS]

<Indicated Bacteria>

Helicobacter pylori susceptible to amoxicillin or clarithromycin

<Indications>

Helicobacter pylori infection in patients with gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, in the stomach after endoscopic resection of early stage gastric cancer, or *Helicobacter pylori* gastritis

[Precautions for indications]

When this drug is used for *helicobacter pylori* gastritis, patients should be confirmed to be positive for *helicobacter pylori* and have a definite diagnosis of *helicobacter pylori* gastritis by endoscopy.

<Case 2> A case of nephrotic syndrome caused by bucillamine

A man in his 70s, Rimatil Tablets (bucillamine) was continuously administered despite the fact that abnormal urine protein and increased serum albumin were noted during its use, until nephrotic syndrome was suspected based on further aggravation of the laboratory values and the patient's complaints of lower leg edema. The case was thus not approved as proper use.

Description in the package insert of Rimatil Tablets (partial excerpts)

[CONTRAINDICATIONS]

Patients with renal disorder [This drug may cause serious renal disorder such as nephrotic syndrome.]

[Important Precautions]

Prior to treatment with this drug, patients should be screened with blood, renal function, and liver function tests, etc. Patients treated with this drug should be closely monitored for clinical symptoms during the treatment, and are required to undergo clinical laboratory tests, including blood testing and urinalysis, on a monthly basis. If laboratory parameters of leukocyte count, platelet count, and urine protein meet any of the following values, administration of this drug should be discontinued, and appropriate measures should be taken.

[Clinically Significant Adverse Reactions]

Acute renal failure (frequency unknown), nephrotic syndrome (e.g., membranous nephropathy) (0.1%): Acute renal failure or nephrotic syndrome (e.g., membranous nephropathy) may occur. Urinalysis and other tests should be performed once a month during the treatment (see "2. Important Precautions"). If any abnormal findings are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.

Healthcare professionals are strongly advised to read through the package insert once again to comply with the proper use.

Alert for Proper Use of Drugs

<https://www.pmda.go.jp/safety/info-services/drugs/calling-attention/properly-use-alert/0004.html>

6. Source of information on the Relief System for Adverse Drug Reactions

Details of this Relief System as well as the Infections derived from Biological Products Relief System can be found on the PMDA's website (<http://www.pmda.go.jp/relief-services/adr-sufferers/0001.html> [only in Japanese]). Furthermore, materials on the Relief System for patients are also available on the website, and healthcare professionals are encouraged to use these materials to disseminate information on the Relief System.

The necessary documents for making claims can be downloaded from the following website and be created electronically using a computer, etc.

If the documents are created electronically using a computer, etc., claimants are requested to also submit paper-based documents and provide an electronic copy of the electronic file using a compact disk, etc.

<http://www.pmda.go.jp/relief-services/adr-sufferers/0004.html> (only in Japanese)

Details of medical certificates and certificates for prescription/use are important information when judging whether the use was proper or not, etc.; therefore, as many details as possible should be included in these documents. Healthcare professionals are also encouraged to use the preparation guidelines for medical certificates.

Please note that the following cases will not be applicable to receiving relief benefits.

- A. Cases of adverse health effects resulting from statutory vaccination practice (Relief System for Injury to Health with Vaccination is applicable in accordance with the Preventative Vaccination Law.)
However, cases of adverse health effects resulting from voluntary vaccinations are applicable for relief benefits under the Relief System.
- B. Cases in which it is clear who is responsible for payment of damages such as MAHs ^{Note 5)}
- C. Cases in which it is necessary to use the pharmaceutical in an amount exceeding the approved dosage for the purpose of saving the patient's life, even if it was recognized beforehand that the adverse health effects may occur ^{Note 6)}
- D. Cases in which the purpose/method of use is not confirmed to be proper (such as cases in which pharmaceuticals are used in other ways than the indications approved by the Minister of Health, Labour and Welfare, or cases in which pharmaceuticals have not been used in accordance with the Precautions of the package inserts)
- E. Cases of adverse health effects resulting from drugs not considered eligible for the Relief System

Pharmaceuticals not considered eligible include:

- i Pharmaceuticals used for the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (anticancer drugs, immunosuppressants, etc.)
 - ii Pharmaceuticals that do not have the possibility to cause ADRs, including pharmaceuticals not used directly on human bodies or pharmaceuticals without pharmacological effects (insecticides, disinfectant agents, in vitro diagnostics, etc.)
- F. Cases of mild adverse health effects (including hospital administration in which treatment equivalent to inpatient care is not required) or cases in which disabilities caused by pharmaceuticals fail to meet the disability criteria under the Relief System, ^{Note 7)} and cases that fail to meet the following criteria: "Disability that results in significant limitation during the patient's activities of daily life (Grade 2)"
- G. Cases in which the deadline for claiming the relief benefits has passed
- H. Other cases that have not been approved by the Pharmaceutical Affairs and Food Sanitation Council, MHLW based on medical and pharmaceutical judgment
- Cases in which the disorders or disabilities are considered to be unlikely caused by ADRs (those that are not considered due to drugs)
 - Cases in which it cannot be judged whether there is a causal relationship or whether pharmaceuticals are used for the proper use and by the proper method, because of insufficient documentation (impossible to judge)

7. Closing comments

Healthcare professionals are encouraged to fully check the necessary alerts in the package inserts before using drugs and to use them properly. Please note that cases in which drugs are not used properly may not be applicable to receive relief benefits under the Relief System even if the adverse health effects are suspected to have been caused by ADRs related to the drugs. On the other hand, off-label uses which are widely known in medical practice, such as those described in the guidelines, may be covered for relief benefits.

If ADRs, etc. occur or if healthcare professionals are consulted by their patients about ADRs, healthcare professionals should provide information on the Relief System to the patient or family members if the adverse health effects are possibly applicable to receiving relief benefits under the Relief System. MHLW/PMDA encourages the continued cooperation from healthcare professionals in preparing documents, such as medical certificates, required to claim these relief benefits.

For the details of the Relief System, see the website below.

<https://www.pmda.go.jp/index.html>

The following consultation service in regard to this Relief System is available (same service provided for Infections derived from Biological Products Relief System).

- Relief System Consultation Service, PMDA

Phone: 0120-149-931 (toll-free)

Office hours: Monday to Friday 9:00-17:00 (excluding national and New Year holidays) E-mail: kyufu@pmda.go.jp

Note 1) From: 2017 Awareness Survey on the Relief System for Adverse Drug Reaction (only in Japanese)

<https://www.pmda.go.jp/relief-services/adr-sufferers/0023.html>

Note 2) From: Annual Report FY 2017 (Pharmaceuticals and Medical Devices Agency)

<https://www.pmda.go.jp/files/000224837.pdf>

Note 3) The periods during which administrative processing cannot be conducted, because of the need for additional or supplemental documents from claimants and medical institutions for the purpose of making medical and pharmaceutical judgments, are excluded from the administrative processing time from the claim submission to the payment approval/rejection decision.

Note 4) The number of cases is based on the number of applicants. Therefore, if the same applicant submits a claim for the same cause after a first claim for it has been submitted, it is counted as 1 case.

Note 5) "Person responsible for payment of damages" typically refers to the person in charge, etc. for accidents due to adulterated drugs such as mutated drugs or contaminated drugs."

Note 6) If the sufferer's acceptance of the ADR that occurred is a socially accepted concept.

Typical situations in which such acceptance is anticipated are as follows:

- (1) The pharmaceutical is used in critical care situations.
- (2) There are no alternative treatment modalities available.
- (3) A higher dose of the pharmaceutical than the usual dose is used.
- (4) The possibility of adverse health effects due to ADRs was recognized in advance.
- (5) Adverse health effects due to ADRs which had been recognized in advance mentioned in (4) occurred.

Whether individual cases will be accepted will be judged based on these typical situations. For the claim to be considered acceptable, similar acceptance in terms of social acceptance must be necessary. In such cases, even if the aforementioned 5 criteria are not all satisfied, cases will be judged based on whether they are in accordance with a typical case from an overall standpoint including other situations or factors, etc.

Note 7) Degree of disability does not meet the criteria of "Disability that prevents a person from performing daily life activities by himself/herself (Grade 1)" or "Disability that results in significant limitations during the patient's activities of daily life (Grade 2)"

Relief Efforts for Human Papilloma Virus Vaccine through the Relief System for Adverse Drug Reactions

1. Introduction

The joint meeting of the Adverse Reactions Review Committee for Preventative/Voluntary Vaccination on the Health Sciences Council and the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council in regard to the human papilloma virus vaccine (hereinafter referred to as “HPV vaccines”) was held on September 17, 2015. During this meeting, results from the national tracking survey were presented. According to the findings, there are people suffering from various symptoms and people who have problems in their daily life or school life.

Based on these results, under the Relief System, MHLW/PMDA have promptly reviewed the relief claims for claimants who claim adverse health effects for symptoms that occurred after administration of HPV vaccines and have taken efforts to increase awareness of the Relief System. By the end of September 2017, there have been 274 of the total 436 patients who had been reviewed who were determined eligible for the Relief System for whom a causal relationship to HPV vaccines could not be ruled out.

MHLW will continue to offer the necessary support to patients while promptly reviewing the relief claims.

2. Relief benefits for adverse health effects due to “Urgent Vaccine Promotion such as for cervical cancer vaccines”

Adverse health effects in people who were vaccinated with vaccines applicable to the relevant promotional business ^{Note)} are regarded to be ADRs based on the review results of the relief benefits. For example, even if the medical care required was not of an extent to be considered inpatient care, such as when patients received treatment on an outpatient basis, the patient may be eligible to receive support for medical expense/medical allowance payments from the Public Foundation of the Vaccination Research Center.

If support for medical expenses/medical allowances is to be provided for the first time for any adverse health effect caused by vaccination in this program, a claim for relief benefits must first be submitted for the Relief System; therefore, healthcare professionals are requested to cooperate with the claimant's procedures (creation of medical certificates, etc.).

Note) Females who are first year junior high school students (approximately 13 years old) to those who are first year high school students (approximately 16 years old) to whom HPV vaccines were administered during the period from November 26, 2010 to March 31, 2013 are possibly eligible to receive relief benefits.

http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/sesshu_youryou.pdf

3. Items to be considered in regard to the necessary documentation when claiming relief benefits under the Relief System for Adverse Drug Reactions in relation to HPV vaccines, etc.

MHLW issued an administrative notice on January 14, 2016 regarding items to be considered in regard to the necessary documentation when claiming relief benefits.

1. About medical certificates

- (1) Medical certificates are only required for medical care related to the adverse health effect the claims are being filed for, regardless of whether the care is provided on an inpatient or outpatient basis. Claimants do not need to request all medical institutions they visited to create medical certificates.
- (2) For the medical certificates, information necessary to judge the causal relationship to the vaccination, such as information regarding the day of vaccination and the clinical course until the onset of symptoms, is considered important and should be provided as far as possible. It is also permissible for the medical institution creating the medical certificate to include other information than treatment (for example, information related to the duration

of clinical practice if the patient consulted multiple medical institutions since the symptoms were not apparent, symptoms that triggered hospital consultation, etc.).

Please also cooperate with the attachment of materials related to other medical institutions (addresses, telephone numbers, days of consultation, medical chart number, name of physician in charge, symptoms that triggered hospital consultation, etc.) even if the material is created by the claimant and not the medical institution or if the materials have only partial information.

2. About certificates for prescription/use

- (1) If the vaccine was administered by the physician or medical institution that created the medical certificate, certificates for prescription are unnecessary.
- (2) If possible, please request vaccination coupons provided prior to vaccination or other reference materials (such as body temperature results, items asked during the medical interview or examination) and attach these to the claims.

From the administrative notice issued on January 14, 2016 by the Safety Division of the MHLW “Items to be considered in regard to the necessary documentation when claiming relief benefits under the Relief System for Adverse Drug Reactions in relation to administration based on “Urgent Vaccination Promotion such as for cervical cancer vaccines”.”

(References)

Notification issued September 30, 2015 “Enhancing consultation/support services for those who developed symptoms after vaccination for HPV infections” (Health Safety Bureau, MHLW Notification No. 0930-7, 27Sports and Youth Bureau, Ministry of Education, Culture, Sports, Science and Technology Notification No. 419)

http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/madoguchi/dl/151116_02.pdf (only in Japanese)

Administrative notice issued on October 22, 2015 by HSD/SD (Request for) Increasing awareness of deadlines for the Relief System for Adverse Drug Reactions claims in relation to administration based on “Urgent Vaccination Promotion such as for cervical cancer vaccines”
<http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/dl/yobou151022-1.pdf> (only in Japanese)

Administrative notice issued on December 1, 2015 by HSD (Request for) Relief benefits for adverse health effects due to Urgent Vaccination Promotion such as for cervical cancer vaccines
<https://www.pmda.go.jp/files/000208632.pdf> (only in Japanese)

Administrative notice issued on January 14, 2016 by SD Items to be considered in regard to necessary documentation when claiming relief benefits under the Relief System for Adverse Drug Reaction in relation to administration based on “Urgent Vaccination Promotion such as for cervical cancer vaccines”
<https://www.pmda.go.jp/files/000209731.pdf> (only in Japanese)

Notification issued on January 15, 2016 for each medical association, etc. Request of cooperation for the Relief System for Adverse Health Effects provided by PMDA (Office of ADR, PSEHB Notification No. 0115-1, and PSEHB/SD Notification No. 0115-1)
<https://www.pmda.go.jp/files/000209915.pdf> (only in Japanese)

About the establishment of Subcommittee on Evaluation of Adverse Reactions of HPV Vaccines
<http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000117420.pdf> (only in Japanese)

3

Revision of Precautions (No. 297)

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 August 21 and September 18, 2018.

1

Antiparkinsonian agents, Psychotropics, Antivirals

Amantadine hydrochloride

Branded name	Symmetrel Tablets 50 mg, 100 mg, Symmetrel Fine Granules 10% (Sun Pharma Japan Limited), and the others
Important precautions	<p>Use of this drug for "Influenza A virus infection"</p> <p><u>Abnormal behaviour has been reported in patients infected with influenza, regardless of the use or non-use, or the type of influenza antiviral drug prescribed.</u></p> <p>Patients and/or their families must be made aware of the following precautionary points to avoid rare accidents including falls due to abnormal behaviour; (1) abnormal behaviour may occur and (2) caregivers should take preventive measures for accidents including falls for at least 2 days <u>after patients develop pyrexia</u> if they are treated at home.</p> <p><u>Severe abnormal behaviour potentially leading to accidents such as falls is known to have been reported to occur with greater frequency in male school-age children/adolescents, and within 2 days after patients develop pyrexia.</u></p>
Adverse reactions (clinically significant adverse reactions)	<p><u>Disturbed consciousness (including coma), psychiatric symptoms (such as hallucination, delusion, delirium, and confusion), convulsions, myoclonus, and abnormal behaviour:</u> Disturbed consciousness (including coma), psychiatric symptoms (such as hallucination, delusion, delirium, and confusion), convulsions, myoclonus may occur. In such cases, appropriate measures including reducing the dosage or discontinuing administration should be taken. Caution should be exercised as these symptoms may occur with particular frequency in patients exhibiting decreased renal function. <u>Abnormal behaviour (such as sudden movement, or wandering) that could result in falls etc. may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and this drug is currently unclear.</u></p>

Oseltamivir phosphate

Branded name	Tamiflu Capsule 75, Tamiflu Dry Syrup 3% (Chugai Pharmaceutical Co., Ltd.), and the others
Important precautions	<p><u>Abnormal behaviour has been reported in patients infected with influenza, regardless of the use or non-use, or the type of influenza antiviral drug prescribed.</u></p> <p><u>Patients and/or their families must be made aware of the following precautionary points to avoid rare accidents including falls due to abnormal behaviour; (1) abnormal behaviour may occur and (2) caregivers should take preventive measures for accidents including falls at least for 2 days after patients develop pyrexia if they are treated at home.</u></p> <p><u>Severe abnormal behaviour potentially leading to accidents such as falls is known to have been reported to occur with greater frequency in male school-age children/adolescents, and within 2 days after patients develop pyrexia.</u></p>
Adverse reactions (clinically significant adverse reactions)	<p>Neuropsychiatric symptoms, abnormal behaviour: Neuropsychiatric symptoms (such as disturbed consciousness, delirium, hallucination, delusion, and convulsion) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken according to the patient's symptoms. <u>Abnormal behaviour (such as sudden movement or wandering) that could result in falls etc. may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and this drug is currently unclear.</u></p>

3

Antivirals

[1] Zanamivir hydrate**[2] Laninamivir octanoate hydrate**

Branded name	[1] Relenza (GlaxoSmithKline K.K.) [2] Inavir Dry Powder Inhaler 20 mg (Daiichi Sankyo Co., Ltd.)
Important precautions	<u>Abnormal behaviour</u> has been reported <u>in patients infected with influenza, regardless of the use or non-use, or the type of influenza antiviral drug prescribed.</u> Patients and/or their families must be made aware of the following precautionary points to avoid rare accidents including falls due to abnormal behaviour; (1) abnormal behaviour may occur and (2) caregivers <u>should take preventive measures for accidents including falls for at least 2 days after patients develop pyrexia</u> if they are treated at home. <u>Severe abnormal behaviour potentially leading to accidents such as falls is known to have been reported to occur with greater frequency in male school-age children/adolescents, and within 2 days after patients develop pyrexia.</u>
Adverse reactions (clinically significant adverse reactions)	<u>Abnormal behaviour:</u> <u>Abnormal behaviour (such as sudden movement or wandering) that could result in falls etc. may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and this drug is currently unclear.</u>

4

Antivirals

Baloxavir marboxil

Branded name	Xofluza Tablets 10 mg, 20 mg (Shionogi & Co., Ltd.)
Important precautions	<u>Abnormal behaviour</u> has been reported <u>in patients infected with influenza, regardless of the use or non-use, or the type of influenza antiviral drug prescribed.</u> Patients and/or their families must be made aware of the following precautionary points to avoid rare accidents including falls due to abnormal behaviour; (1) abnormal behaviour may occur and (2) caregivers <u>should take preventive measures for accidents including falls for at least 2 days after patients develop pyrexia</u> if they are treated at home. <u>Severe abnormal behaviour potentially leading to accidents such as falls is known to have been reported to occur with greater frequency in male school-age children/adolescents, and within 2 days after patients develop pyrexia.</u>
Adverse reactions (clinically significant adverse reactions)	<u>Abnormal behaviour:</u> <u>Abnormal behaviour (such as sudden movement or wandering) that could result in falls etc. may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and this drug is currently unclear.</u>

Favipiravir

Branded name	Avigan Tablets 200 mg (Toyama Chemical Co., Ltd.)
Important precautions	<p><u>Abnormal behaviour</u> has been reported in patients infected with influenza, regardless of the use or non-use, or the type of influenza antiviral drug prescribed.</p> <p>Patients and/or their families must be made aware of the following precautionary points to avoid rare accidents including falls due to abnormal behaviour; (1) abnormal behaviour may occur and (2) caregivers <u>should take preventive measures for accidents including falls</u> for at least 2 days <u>after patients develop pyrexia</u> if they are treated at home.</p> <p><u>Severe abnormal behaviour potentially leading to accidents such as falls is known to have been reported to occur with greater frequency in male school-age children/adolescents, and within 2 days after patients develop pyrexia.</u></p>
Adverse reactions (clinically significant adverse reactions)	<p><u>Abnormal behaviour:</u> <u>Abnormal behaviour (such as sudden movement or wandering) that could result in falls etc. may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and this drug is currently unclear.</u></p>

Peramivir hydrate

Branded name	Rapiacta 300 mg Bag for Intravenous Drip Infusion, Rapiacta 150 mg Vial for Intravenous Drip Infusion (Shionogi & Co., Ltd.)
Important precautions	<p><u>Abnormal behaviour</u> has been reported in patients infected with influenza, regardless of the use or non-use, or the type of influenza antiviral drug prescribed.</p> <p>Patients and/or their families must be made aware of the following precautionary points to avoid rare accidents including falls due to abnormal behaviour; (1) abnormal behaviour may occur and (2) caregivers <u>should take preventive measures for accidents including falls</u> for at least 2 days <u>after patients develop pyrexia</u> if they are treated at home.</p> <p><u>Severe abnormal behaviour potentially leading to accidents such as falls is known to have been reported to occur with greater frequency in male school-age children/adolescents, and within 2 days after patients develop pyrexia.</u></p>
Adverse reactions (clinically significant adverse reactions)	<p><u>Abnormal behaviour:</u> <u>Abnormal behaviour (such as sudden movement or wandering) that could result in falls etc. may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and this drug is currently unclear.</u></p>

7

Antineoplastics-Miscellaneous

Radium (²²³Ra) chloride

Branded name Xofigo Injection (Bayer Yakuhin, Ltd.)

Important precautions A clinical study investigating administration of this drug or a placebo in combination with abiraterone acetate plus prednisone (currently unapproved in Japan) or prednisolone to chemotherapy-naïve patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer accompanied by bone metastases showed a tendency for a higher mortality rate and incidence of bone fracture after receiving this drug compared to the patients who were given a placebo. Based on these findings, co-administration of this drug with abiraterone acetate and prednisolone is not recommended in chemotherapy-naïve patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer accompanied by bone metastases.

8

Antineoplastics-Miscellaneous

Sunitinib malate

Branded name Sutent Capsule 12.5 mg (Pfizer Japan Inc.)

Adverse reactions (clinically significant adverse reactions) **Acute cholecystitis:** Acute cholecystitis, including acalculous cholecystitis, may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as suspension of administration should be taken.

9

Acting mainly on gram-positive and gram-negative bacteria

Antibiotics-Miscellaneous

[1] Ampicillin hydrate**[2] Bacampicillin hydrochloride****[3] Ampicillin sodium/cloxacillin sodium hydrate**

Branded name [1] Viccillin Capsules 250 mg, Viccillin Dry Syrup 10% (Meiji Seika Pharma Co., Ltd.)
[2] Pengood Tablets 250 mg (Nichi-Iko Pharmaceutical Co., Ltd.)
[3] Viccillin-S100 for Injection, S500 for Injection, S1000 for Injection (Meiji Seika Pharma Co., Ltd.)

Adverse reactions (clinically significant adverse reactions) **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), or acute generalized exanthematous pustulosis:** Toxic epidermal necrolysis, oculomucocutaneous syndrome, or acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored, and if such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

10

Acting mainly on gram-positive and gram-negative bacteria

Ampicillin sodium**Branded name**

Viccillin 0.25 g for Injection, 0.5 g for Injection, 1 g for Injection, 2 g for Injection (Meiji Seika Pharma Co., Ltd.)

**Adverse reactions
(clinically significant
adverse reactions)**

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), or acute generalized exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, or acute generalized exanthematous pustulosis may occur. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

11

Acting mainly on gram-positive and gram-negative bacteria

Sultamicillin tosilate hydrate**Branded name**

Unasyn Tablets 375 mg, Unasyn Fine Granules for Pediatric Use 10% (Pfizer Japan Inc.)

**Adverse reactions
(clinically significant
adverse reactions)**

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, or exfoliative dermatitis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, acute generalized exanthematous pustulosis, or exfoliative dermatitis may occur. Patients should be carefully monitored and if such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

12

Antibiotics-Miscellaneous

Ampicillin hydrate/cloxacillin sodium hydrate**Branded name**

Viccillin-S Combination Tablets (Meiji Seika Pharma Co., Ltd.)

**Adverse reactions
(clinically significant
adverse reactions)**

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), or acute generalized exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, or acute generalized exanthematous pustulosis may occur. If such symptoms are observed, administration of this drug should be discontinued.

13

Antivirals

Dolutegravir sodium

Branded name	Tivicay Tablets 50 mg (ViiV Healthcare K.K.)
Important precautions	<u>Hepatic impairment and jaundice may occur. Patients should be carefully monitored through methods such as periodic liver function tests. In clinical studies, the frequency of cases of initial or continuous elevation in transaminase levels was higher among patients with hepatitis B and C virus co-infection compared with patients without co-infection.</u>
Adverse reactions (clinically significant adverse reactions)	<u>Hepatic impairment, jaundice:</u> <u>Hepatic impairment accompanied with elevation in AST, ALT, or bilirubin levels, and jaundice may occur. If these or any other abnormalities are observed, appropriate measures such as discontinuing administration should be taken.</u>

14

Antivirals

Dolutegravir sodium/abacavir sulfate/lamivudine

Branded name	Triumeq Combination Tablets (ViiV Healthcare K.K.)
Important precautions	<u>Hepatic impairment and jaundice may occur. Patients should be carefully monitored through methods such as periodic liver function tests. In clinical studies, the frequency of cases of initial or continuous elevation in transaminase levels was higher among patients with hepatitis B and C virus co-infection in association with administration of dolutegravir compared with patients without co-infection.</u>
Adverse reactions (clinically significant adverse reactions)	<u>Hepatic impairment, jaundice:</u> <u>Hepatic impairment accompanied with elevation in AST, ALT, or bilirubin levels, and jaundice may occur. If these or any other abnormalities are observed, appropriate measures such as discontinuing administration should be taken.</u>

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 ADR data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of August 31, 2018)

◎: Products for which EPPV was initiated after August 1, 2018

Nonproprietary name Branded name on		Name of the MAH	Date of EPPV initiate
◎	Obinutuzumab (genetical recombination) Gazyva Intravenous Infusion 1000 mg	Chugai Pharmaceutical Co., Ltd.	August 29, 2018
◎	Durvalumab (genetical recombination) Imfinzi Injection 120 mg, 500 mg	AstraZeneca K.K.	August 29, 2018
◎	Ipilimumab (genetical recombination) *1 Yervoy Injection 50 mg	Bristol-Myers Squibb K.K.	August 21, 2018
◎	Nivolumab (genetical recombination) Opdivo I.V. Infusion 20 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	August 21, 2018
◎	Tedizolid phosphate Sivextro Tablets 200 mg, Sivextro for iv infusion 200 mg	Bayer Yakuhin, Ltd.	August 21, 2018
◎	Condoliase Hernicore 1.25 Units for Intradiscal Inj.	Seikagaku Corporation	August 1, 2018
	Fosravuconazole L-lysine ethanolate Nailin Capsules 100 mg	Sato Pharmaceutical Co., Ltd.	July 27, 2018
	Canakinumab (genetical recombination) *2 Ilaris for S.C. Injection 150 mg, Ilaris Solution for S.C. Injection 150 mg	Novartis Pharma K.K.	July 2, 2018
	Olaparib*3 Lynparza Tablets 100 mg, 150 mg	AstraZeneca K.K.	July 2, 2018
	Japanese cedar pollen extract Cedarcure Japanese Cedar Pollen Sublingual Tablets 2,000 JAU, 5,000 JAU	Torii Pharmaceutical Co., Ltd.	June 29, 2018
	Ibuprofen L-lysine Ibulief I.V. Injection 20 mg	Senju Pharmaceutical Co., Ltd.	June 14, 2018
	Rasagiline mesilate Azilect Tablets 0.5 mg, 1 mg	Takeda Pharmaceutical Company Limited.	June 11, 2018
	Sirolimus Rapalimus Gel 0.2%	Nobelpharma Co., Ltd.	June 6, 2018
	Pemafibrate Parmodia Tab. 0.1 mg	Kowa Company, Ltd.	June 1, 2018

Nonproprietary name		Name of the MAH	Date of EPPV initiate
Branded name on			
	Migalastat hydrochloride Galafold Capsules 123 mg	Amicus Therapeutics, Inc.	May 30, 2018
	Letermovir Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	May 28, 2018
	Mepolizumab (genetical recombination) ^{*4} Nucala for S.C. Injection 100 mg	GlaxoSmithKline K.K.	May 25, 2018
	Ipilimumab (genetical recombination) Yervoy Injection 50 mg	Bristol-Myers Squibb K.K.	May 25, 2018
	Nivolumab (genetical recombination) Opdivo I.V. Infusion 20 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	May 25, 2018
	Botulinum toxin type A ^{*5} Botox for Injection 50 Units, 100 Units	GlaxoSmithKline K.K.	May 25, 2018
	Tofacitinib citrate ^{*6} Xeljanz Tablets 5 mg	Pfizer Japan Inc.	May 25, 2018
	Emicizumab (genetical recombination) Hemlibra Subcutaneous Injection 30 mg, 60 mg, 90 mg, 105 mg, 150 mg	Chugai Pharmaceutical Co., Ltd.	May 22, 2018
	Guselkumab (genetical recombination) Tremfya Subcutaneous Injection 100 mg Syringe	Janssen Pharmaceutical K.K.	May 22, 2018
	Evocalcet Orkedia Tablets 1 mg, 2 mg	Kyowa Hakko Kirin Co., Ltd.	May 22, 2018
	Hydromorphone hydrochloride Naruvein Injection 2 mg, 20 mg	Daiichi Sankyo Propharma Co., Ltd.	May 16, 2018
	Bedaquiline fumarate Sirturo Tablets 100 mg	Janssen Pharmaceutical K.K.	May 8, 2018
	Ezetimibe/atorvastatin calcium hydrate Atozet Combination Tablets LD, HD	MSD K.K.	April 23, 2018
	Dupilumab (genetical recombination) Dupixent S.C. Injection 300 mg Syringe	Sanofi K.K.	April 23, 2018
	Elobixibat hydrate Goofice Tablets 5 mg	EA Pharma Co., Ltd.	April 19, 2018
	Olaparib Lynparza Tablets 100 mg, 150 mg	AstraZeneca K.K.	April 18, 2018
	Inotuzumab ozogamicin (genetical recombination) Besponsa Injection 1 mg	Pfizer Japan Inc.	April 18, 2018
	Benralizumab (genetical recombination) Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	April 18, 2018
	Brexpiprazole Rexulti Tablets 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	April 18, 2018
	Atezolizumab (genetical recombination) Tecentriq I.V. Infusion 1200 mg	Chugai Pharmaceutical Co., Ltd.	April 18, 2018
	Romidepsin Istodax Injection 10 mg	Celgene Corporation	April 18, 2018
	Baloxavir marboxil Xofluza Tablets 10 mg, 20 mg	Shionogi & Co., Ltd.	March 14, 2018

- *1 Radically unresectable or metastatic renal cell carcinoma
- *2 Systemic-onset juvenile idiopathic arthritis that does not adequately respond to existing treatments
- *3 Unresectable or recurrent germline *BRCA*-mutated, HER2-negative metastatic breast cancer previously treated with chemotherapy
- *4 Eosinophilic granulomatosis with polyangiitis that does not adequately respond to existing treatments
- *5 Spasmodic dysphonia
- *6 Remission induction or maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who were not sufficiently responsive to conventional treatments)