Pharmaceuticals and Medical Devices Safety Information

No. 347 October 2017

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on 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 available in Japanese language).

Available information is listed here

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Published by
Ministry of Health, Labour and Welfare

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. 347 October 2017

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Summary of the Relief System for Adverse Drug Reaction and Request of Cooperation for the System**		While the number of applications and payments for the Relief System for Adverse Drug Reaction has increased in recent years, awareness among the general public in fiscal year 2016 was low. Therefore, this section will introduce the overview of the Relief System in order to ensure widespread understanding.	5
2	**Important Safety Information**	*P* *C*	Dabigatran etexilate methanesulfonate: Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated September 12, 2017, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.	17
3	**Revision of Precautions (No. 288)**	*P*	Dabigatran etexilate methanesulfonate (and 2 others)	20
4	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of August 31, 2017.	21

P: Revision of Precautions, *C*: Case Reports

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

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
Anti-HBs	Anti-Hepatitis B surface
Anti-HCV	Anti-Hepatitis C virus
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
ChE	Cholinesterase
CK	Creatine kinase
Cl	Chloride
cpm	Count per minute
Cre	Creatinine
CRP	C-reactive protein
CT	Computed tomography
D-Bil	Direct bilirubin
DIHS	Drug-induced hypersensitivity syndrome
DLST	Drug lymphocyte stimulation test
EPPV	Early Post-marketing Phase Vigilance
FFP	Fresh frozen plasma
FY	Fiscal year
Hb	Hemoglobin
HDL-C	High-density lipoprotein cholesterol
HPV	Human papilloma virus
HSD	Health Service Division
Ht	Hematocrit
K	Potassium
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Na	Sodium
NH3	Ammonia
OTC	Over-the-counter
PLT	Platelet
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PT	Prothrombin time
PT (INR)	Prothrombin time (international normalized ratio)
RBC	Red blood cell count
RCC-LR	Red cells concentrates-leukocytes reduced
S.I	Stimulation index
SD	Safety Division
T-Bil	Total bilirubin
TC	Total cholesterol
TG	Triglyceride
TP	Total protein

WBC	White blood cells
γ-GT	gamma-glutamyl transpeptidase

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Summary of the Relief System for Adverse Drug Reaction and Request of Cooperation for the System

1. Introduction

The Relief System for Adverse Drug Reaction (ADR) (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 reaction 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 part 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 using biological products despite proper use. Furthermore, adverse reaction to regenerative medical products and infections, etc. acquired through use of such products is now being covered by the Relief System since November 25, 2014.

The number of applications for the Relief System and payments of relief benefits has been increasing in recent years, and, since the establishment of the Relief System in 1980 until fiscal year (FY) 2016, 19 900 cases have been granted relief benefits.

2. Awareness on the Relief System for Adverse Drug Reaction Note 1)

Awareness of the Relief System among the general public in FY2016 was 29.4% in total: 8.6% who answered that they "were aware" of the Relief System and 20.9% 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 they have suffered because they are unaware of the Relief System.

On the other hand, the awareness among healthcare professionals was 82.4% in total: 57.9% who answered that they "were aware" of the Relief System and 24.5% who answered that they "have heard about" the Relief System. By occupational category, the awareness was 92.0% of physicians, 97.5% of pharmacists, 59.6% of nurses, and 78.6% of dentists.

Among healthcare professionals who were aware of the Relief System, the proportion of those who were involved in a filing procedure was 8.7% in total: 8.8% of physicians, 12.2% of pharmacists, 5% of nurses, and 5.3% of dentists. 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 will utilize the Relief System and should also cooperate with preparation of medical certificates, etc. when people suffering from adverse health effects file an application for compensation.

Note 1) From "2016 Awareness Survey on the Relief System for Adverse Drug Reaction" (only available in Japanese language)
http://www.pmda.go.jp/relief-services/adr-sufferers/0023.html

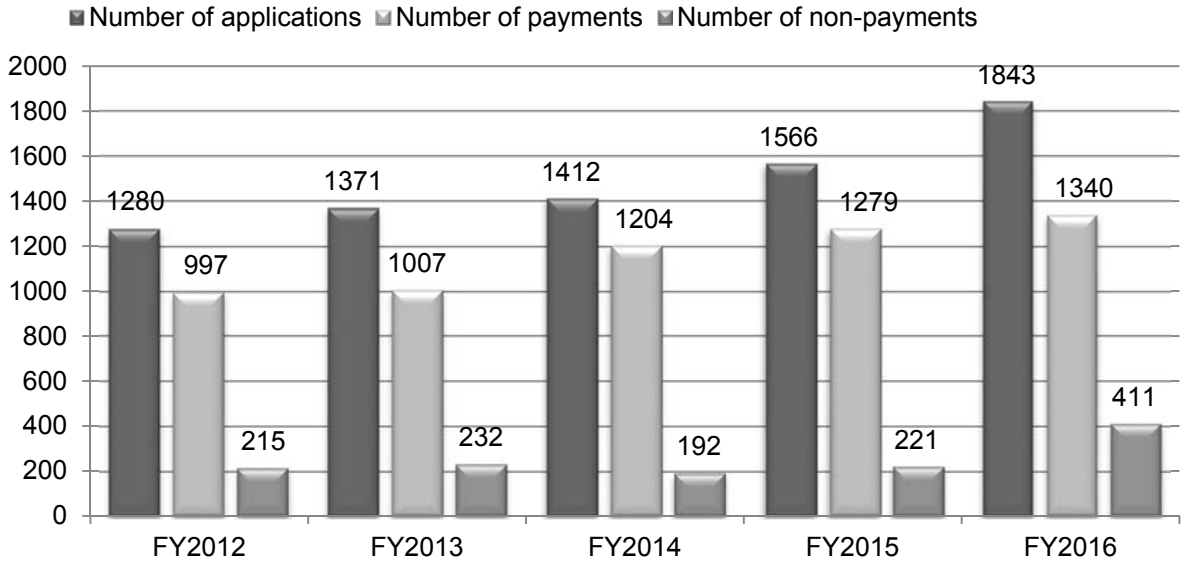
3. Status of payment/non-payment cases in the Relief System

The number of applications for the Relief System and payments of relief benefits has been increasing. The annual changes from FY2012 to FY2016 are shown in Figure 1. The number of applications in FY2016 was 1 843, the number of payments was 1 340, and the number of non-payments was 411. Details of reasons for non-payments are shown in Figure 2.

In addition, the goal of standard administrative processing time[Note 2)] 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 FY2016 was 67.4%.

Note 2) 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 purposes of making medical and pharmaceutical judgments, are excluded from the administrative processing time from claim submission to payment approval/rejection judgments.

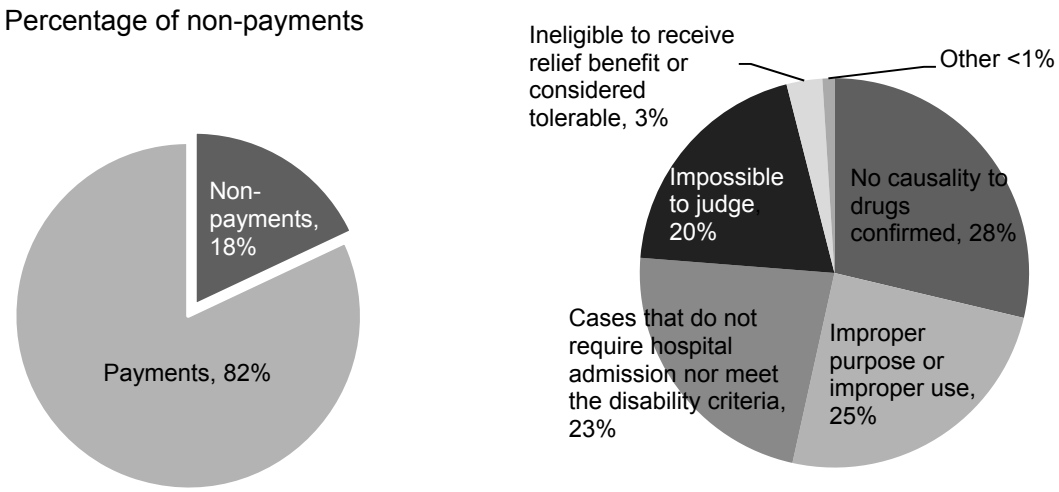
Figure 1. Number of payments and non-payments under the Relief System for Adverse Drug Reaction (FY2012 to FY2016)



(Explanation for the figure)

* The number of cases is based on the number of applicants. Therefore, if there is a claim submitted for the same cause after the first claim was 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 the receipt of the application to the decision on benefit payments.

Figure 2. Reasons for non-payments between FY2012 and FY2016



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 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 (http://www.pmda.go.jp/english/relief-services/0002.html).

[Types and amounts of relief benefits (as of April 01, 2017)]

Medical Expenses (costs borne by the patients, not including health insurance payments)
- Actual costs of treatment for disease caused by ADRs etc. will be compensated.

Medical Allowance (34,300 to 36,300 yen per month)
- Benefits are provided for costs other than medical costs for treatment of diseases caused by ADRs.

Disability Pension (Grade 1: 2,752,800 yen per year, Grade 2: 2,203,200 yen per year)
- Benefits are provided to compensate for living costs, etc., of patients aged 18 or older, who suffer from a certain degree of disabilities caused by ADRs, etc.

Pension for Raising Children with disabilities (Grade 1: 860,400 yen per year, Grade 2: 688,800 per year)
- Benefits are provided for people who are responsible for raising children under 18 who suffer from a certain degree of disabilities caused by ADRs, etc.

Bereaved Family Pension (2,408,400 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 (7,225,200 yen)
- Benefits are provided for bereaved families for condolence and sympathy following the death from ADRs, etc. of their family member who is not the main provider.

Funeral Expenses (206,000 yen)
- Benefits are provided for the costs of holding funeral for people who died from ADRs, etc.

[Cases of relief benefit payments]
<Case 1> Case provided Medical Expenses and Medical Allowance for drug-induced hypersensitivity syndrome (DIHS) due to an antiepileptic agent

After carbamazepine tablets (Tegretol) was taken by a male patient in his 40s, the patient developed DIHS and was admitted to the hospital for treatment. Medical Expenses and Medical Allowance were paid.

<Case 2> Case provided Bereaved Family Pension and Funeral Expenses for anaphylactic shock caused by an X-ray contrast agent.

Immediately after ioversol (Optiray) was injected to a male patient in his 60s, the patient developed anaphylactic shock, resulting in cardiopulmonary arrest and death. Bereaved Family Pension and Funeral Expenses were paid.

<Case 3> Case provided Disability Pension for retinopathy caused by psychotropics

After chlorpromazine/promethazine combination product (1) and chlorpromazine/promethazine combination product (2) (Vegetamin-A combination tablets and Vegetamin-B combination tablets) were taken by a female patient in her 50s, the patient developed retinopathy and visual impairment. Disability Pension was paid.

<Case 4> Case provided Medical Expenses and Medical Allowance due to mucocutaneous ocular syndrome (Stevens-Johnson syndrome) caused by an OTC drug

After Lulu Attack EX was taken by a male patient in his 20s, the patient developed mucocutaneous ocular syndrome (Stevens-Johnson syndrome) and was admitted to the hospital for treatment. Medical Expenses and Medical Allowance were paid.

5. Cases where proper use of pharmaceuticals could not be confirmed

Of the 1 270 non-payment cases between FY2012 to FY2016 Note 3), the reason for non-payment in approximately one-quarter of them was that proper purpose or method of use of the pharmaceutical could not be confirmed (Figure 2). The reason why the method of use was not considered proper most recently (in the last year or so) is presented in this section together with the description provided in package inserts or specific cases. Table 1 shows the most common pharmaceuticals for which method of use was not considered proper.

Note 3) The number of cases is based on the number of applicants. Therefore, if there is a claim submitted for the same cause after the first claim was submitted, it is counted as 1 case.

Table 1. Number of cases for which method of use of the pharmaceutical was not considered proper (FY2012 to FY2016)

Name of causative drug	FY2012	FY2013	FY2014	FY2015	FY2016	Total (cases)
Lamotrigine	43	26	24	23	24	140
Thiamazole	7	1	2	5	3	18
Lithium carbonate	2	3	0	1	8	14
Other	36	43	29	25	19	152
Total (cases)	88	73	55	54	54	324

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

Cases using lamotrigine (Lamictal Tablets) account for a large majority of cases for which method of use of the pharmaceutical was not considered proper.

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

Improper use of lamotrigine

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

Nonetheless, many claims have ended up as non-payment because proper use was not confirmed.

Many of the cases where payment was not approved due to improper use included prescription of excessive dosages during initial administration or during titration up to a maintenance dose, or non-adherence to dose increase intervals.

Dosage and administration of lamotrigine are closely regulated in terms of dosages and dose increase intervals depending on specific indications and concomitant pharmaceuticals.

Dear Healthcare Professionals Letter of Rapid Safety Communication in February 2015 "Serious skin disorders caused by Lamictal Tablets" (excerpt)

Healthcare professionals should comply with the dosage and administration.

The incidence of skin disorders increases when this drug is administered more frequently or at a higher dose than approved.

- During the initial administration, this drug should not be used more frequently or at higher doses than the approved dosage and administration.
- When used concomitantly with sodium valproate, this drug should only be administered on alternate-days for the first two weeks (only for adult patients).
- This drug should not be used more frequently or at higher doses than the approved dosage and administration during dose titration until maintenance dosage is achieved.
- A dose increase should not be attempted earlier than the specified timing.

Healthcare professionals should make an effort towards early detection and treatment of skin disorders.

The following symptoms in addition to rash may indicate the development of serious skin disorders. Administration of this drug should be discontinued immediately if such symptoms are observed.

- ○ Pyrexia (38°C and above)
- ○ Lip/oral mucosa erosion
- ○ General malaise
- ○ Ocular hyperaemia
- ○ Pharyngodynia
- ○ Lymphadenopathy, etc.

- Delay in treatment of skin disorders might lead to a serious outcome. Healthcare professionals should consult with a dermatologist at an early stage, and appropriate measures should be taken.
- Patients or family members should be advised to seek medical attention immediately and should inform the doctor/pharmacist that they are being treated with this drug if a rash and/or the above symptoms occur.

For lamotrigine, if the starting dose is higher than the dosage and administration described in the package insert or the timing of a dose increase is earlier, method of use will not be considered proper.

As an example, Figure 3 explains, in line with the description of the package inserts, the concept of proper use concerning the dosage and administration of lamotrigine in terms of concomitant medications when used for suppression of recurrent/relapsed mood episodes in patients (adults) with bipolar disorder.

Attention is required for dosage and administration of lamotrigine which vary depending on the concomitant medication. First, please check intended concomitant medications against those listed in Figure 3 from the top to the bottom. If any one is identified in the list, then select the dosage and administration for lamotrigine with the medication in Table 2.

Figure 3. Examples of concomitant medications with lamotorigine (only those with indications for epilepsy and bipolar disorder extracted)

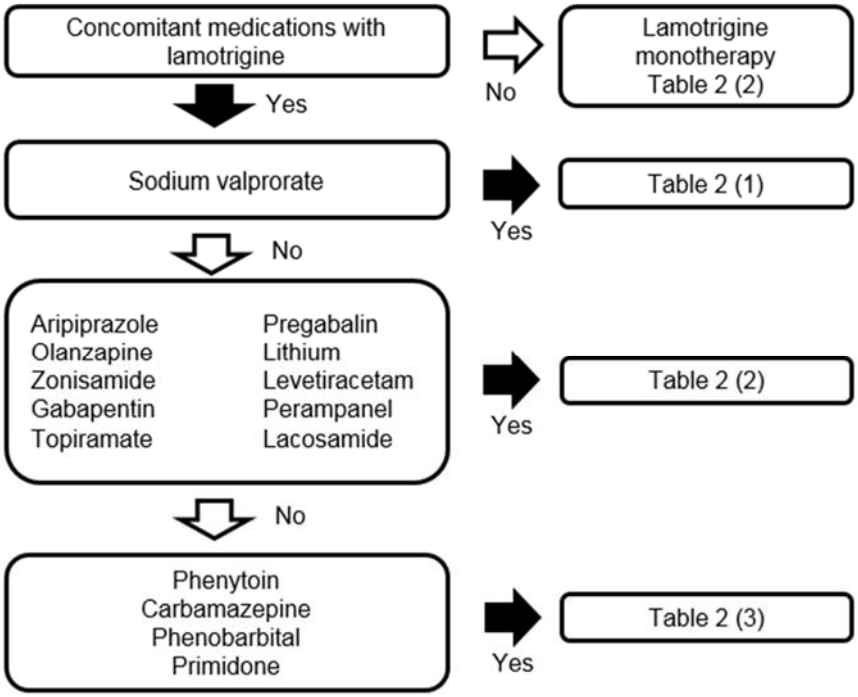


Table 2. Dosage and administration of lamotrigine at the start of administration (when used for suppression of recurrent/relapsed mood episodes in patients with bipolar disorder: Adults, up to Week5)

Dosage and administration of concomitant medication (see Figure 3)	Week 1/2	Week 3/4	Week 5
(1)	25 mg once every2 days	25 mg/day	50 mg/day
(2)	25 mg/day	50 mg/day	100 mg/day
(3)	50 mg/day	100 mg/day	200 mg/day

The Figure 3 above lists examples of concomitant medications contained in the package inserts of lamotrigine For actual use of concomitant medications, package inserts should be carefully checked including notes on medications falling under “when used concomitantly with medications that induce glucuronidation of this drug,” or “when used concomitantly with medications other than those that induce glucuronidation of this drug” as noted in the package inserts.

(2) Case where required tests are not performed

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

Tests not conducted when using lithium carbonate

Lithium carbonate may cause poisoning when overdosed, and therefore it is required that lithium carbonate be used while periodically measuring the lithium serum concentration and assessing the trough level. Also, lithium carbonate is contraindicated in patients prone to develop lithium retention such as patients with renal impairment. Alerts have been issued in many ways using notifications on proper use, etc. from PMDA and various materials, but cases of non-conduct of tests have still been reported.

Cases Case of bradycardia with use of lithium carbonate

Lithium serum concentration was not measured at all for a male patient in his 70s for approximately five years after initiating lithium carbonate treatment. Renal impairment was observed but administration was continued after that; therefore, method of use was not considered proper.

Description of package insert of lithium carbonate

[CONTRAINDICATIONS]
3. Patients who are prone to develop lithium retention [Toxicity of lithium may be increased]
(1) Patients with renal impairment
[PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION]
Overdosage may cause poisoning. This drug should be used while assessing the trough level* based on the results of measurement of the serum concentration of lithium approximately once a week during initial administration or until a maintenance dose is determined when the dosage is increased or approximately once every 2 or 3 months during treatment at the maintenance dose. (snip)
[Clinically Significant Adverse Reactions]
3. Sick sinus syndrome, severe bradycardia:
Sick sinus syndrome or severe bradicardia 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.

In order to detect ADRs early and prevent them from becoming serious, healthcare professionals are encouraged to use the drug properly according to the “Precautions for use” as tests for early detection of ADRs and explanations to patients regarding the need for such tests are considered important.

Alert for Proper Use of Drugs
http://www.pmda.go.jp/english/safety/info-services/drugs/properly-use-alert/0001.html

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

Details of this Relief System as well as the Infections derived from Biological Products Relief System can be found on PMDA’s website (http://www.pmda.go.jp/relief-services/adr-sufferers/0001.html [only available in Japanese language]). 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.

Necessary documents for making claims can be downloaded from the following website and can be created using a computer, etc.
Furthermore, if the documents are created using a computer, etc., claimants are requested to submit the paper-based documents as well as 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 available in Japanese language)
Details of medical certificates and certificates for prescription/use are important information when judging whether or not use was proper, 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 receive 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 where it is clear who is responsible for payment of damages such as MAHs [Note 4)]
C. Cases where 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 adverse health effects may occur [Note 5)]

D. Cases where purpose/method of use is not confirmed to be proper (such as cases where pharmaceuticals are used in ways other than the indications approved by the Minister of Health, Labour and Welfare, or cases where pharmaceuticals have not been used in accordance with the Precautions of 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 in 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 where disabilities caused by pharmaceuticals fail to meet the disability criteria under the Relief System Note 6)

Or cases that fail to meet the following criteria: “Disability that results in significant limitation during his/her daily life performance (Grade 2)”

G. Cases where 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 where the disorders or disabilities are considered to be unlikely to be caused by ADRs (those that are not considered to be due to drugs)
- Cases where it cannot be judged whether there are causalities or whether pharmaceuticals are used for the proper use and with the proper method, because of insufficient documentation (impossible to judge)

Note 4) “Person responsible for payment of damages” typically refers to person in charge, etc. for accidents due to adulterated drugs such as mutated drugs or contaminated drugs.”

Note 5) If the sufferer’s acceptance towards 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 for critical care situations.
(2) There are no alternative treatment modalities available.
(3) A higher dose of the pharmaceutical than the recommended 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 were recognized in advanced mentioned in (4) occurred.

Whether individual cases will be accepted will be judged based on these typical situations. In order 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 6) 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 limitation during his/her daily life performance (Grade 2)”

7. Closing comments

Healthcare professionals are encouraged to fully check necessary alerts in the package inserts before using drugs and to use them properly. Please note that cases where 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 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 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.
http://www.pmda.go.jp/english/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

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

1 Introduction

The joint meeting of the Adverse Reaction 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 (cervical cancer prevention vaccines, 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 troubled 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.

MHLW will continue to offer necessary support for 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 sufficient 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 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, claims for relief benefits must first be submitted for the Relief System; therefore, healthcare professionals are requested to cooperate with claimant's procedures (creating medical certificates, etc.).

Note) Females who are first year junior high students (approximately 13 years old) to those who are first year high school students (approximately 16 years old) in whom HPV vaccines were administered in 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 (only available in Japanese language)

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

MHLW issued an administrative notice on January 14, 2016 regarding items to be considered in regard to 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 for medical certificates to be created by all medical institutions they visited.
   (2) For the medical certificates, information necessary to judge the causal relationship with the vaccination, such as information regarding day of vaccination and the clinical course until onset of symptoms, is considered important and should be provided as much as possible. Furthermore, it is permissible for the medical institution creating the

medical certificate to include information other than treatment (for example, information related to the duration of clinical practice where the patient consulted multiple medical institutions since the symptoms were not apparent, symptoms that triggered hospital consultation, etc.).

Please also cooperate in attaching materials related to other medical institutions (addresses, telephone numbers, day 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 materials that only have 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 medical interview or examined) 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 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"."

(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 available in Japanese language)
Administrative notice issued on October 22, 2015 by HSD/SD "(Request for) Increasing awareness of deadlines for the Relief System for Adverse Drug Reaction 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 available in Japanese language)
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"
http://www.pmda.go.jp/files/000208632.pdf (only available in Japanese language)
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""
http://www.pmda.go.jp/files/000209731.pdf (only available in Japanese language)
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)
http://www.pmda.go.jp/files/000209915.pdf (only available in Japanese language)
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 available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated September 12, 2017, the contents of important revisions and a case summary that served as the basis for these revisions are provided in this section.

1 Dabigatran etexilate methanesulfonate

Brand name (name of company)	Prazaxa Capsules 75 mg, 110 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic category	Anticoagulants
Indications	Reduction in the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	Acute hepatic failure, hepatic function disorder, and jaundice: Acute hepatic failure, hepatic function disorder, and jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 2 months (April 2014 to June 2017). Cases related to acute hepatic failure, hepatic function disorder, and jaundice: 1 case (no fatal case) The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 240 000 Launched in Japan: March 2011

Case summary

Patient		Daily dose/ Treatment duration	Adverse reactions	
Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
Female 70s	Atrial fibrillation (alcohol consumption, hypothyroidism, hyperuricemia)	220mg for 5 days	Acute liver failure, acutekidney injury	
			Date unknown	Administration of levothyroxine sodium hydrate 75 μg/day was initiated.
			Date unknown	Administration of aspirin 100 mg/day was initiated.
			Day 1 of administration	Creatinine clearance was 46.0 mL/min as estimated by the Cockcroft-Gault method. Since atrial fibrillation was observed, dabigatran etexilate methanesulfonate 220 mg/day (twice daily) and disopyramide 300 mg/day (twice daily) were prescribed at the previous hospital. Administration of aspirin was discontinued due to inadequate response.
			Day 3 of administration	Onset of congestive cardiac failure. Due to a tendency toward heart failure, furosemide 10 mg/day was prescribed at the previous hospital.
			Day 5 of administration (day of discontinuation)	Onset of acute hepatic failure and acute kidney injury. The patient visited the emergency outpatient unit of this hospital for the treatment of heart failure and atrial fibrillation. Due to liver disorder found in a blood test, the patient was admitted to the hospital. Diagnosed with drug-induced liver disorder. Administration of dabigatran etexilate methanesulfonate, disopyramide, and furosemide was discontinued because these were considered to be suspected drugs.
			1 day after discontinuation	Plasma exchange and hemodialysis were performed due to no improvement of liver disorder and renal impairment. Transfusion of FFP and RCC-LR started (until 6 days after discontinuation). Symptoms of hepatic encephalopathy: None
			2 days after discontinuation	Day 2 of plasma exchange
			3 days after discontinuation	Onset of right groin haematoma (non-serious). Day 3 of plasma exchange. Renal impairment and liver disorder improved. Spontaneous urination was also present.
			14 days after discontinuation	DLST confirmed that dabigatran etexilate methanesulfonate was the causative agent. Treatment for heart failure and atrial fibrillation was performed with azosemide and warfarin potassium. After that, rehabilitation was performed.
			Unknown date after discontinuation (between 15 and 39 days after discontinuation)	Acute hepatic failure: Resolving.
			40 days after discontinuation	Congestive heart failure, acute kidney injury, right groinhaematoma: Resolving. The patient was discharged from the hospital.
			Date unknown	Administration of levothyroxine sodium hydrate was ongoing.

Laboratory Examination

		Day 1 of administration	Day 5 of administration (day of discontinuation)	1 day after discontinuation	4 days after discontinuation	14 days after discontinuation	17 days after discontinuation	38 days after discontinuation
RBC	(x 104/μL)	381	344	-	262	340	-	-
Hb	(g/dL)	12.3	11.5	-	8.4	10.8	-	-
Ht	(%)	39.6	36.1	-	25.6	33.7	-	-
WBC	(/μL)	6410	10400	-	6600	8000	-	-
PLT	(x 104/μL)	-	4.5	-	5	22.1	-	19.6
PT	(sec)	-	96.8	-	12.7	14.2	-	-
AST	(IU/L)	56	8501	-	141	43	-	31
ALT	(IU/L)	56	3717	-	189	45	-	13
ALP	(IU/L)	363	382	-		236	-	293
LDH	(IU/L)	335	7915	-	293	326	-	-
γ-GT	(IU/L)	119	172	-	38	65	-	76
T-Bil	(mg/dL)	-	2.36	2.87	2.56	2.76	-	1.12
TC	(mg/dL)	144	119	-	-	-	-	-
HDL-C	(mg/dL)	50	32	-	-	-	-	-
TG	(mg/dL)	-	79	-	-	-	-	-
TP	(g/dL)	7	6.6	-	5.4	6.8	-	-
Alb	(g/dL)	4.2	3.9	-	3.2	3.1	-	3.6
Blood glucose	(mg/dL)	146	65	-	90	97	-	-
BUN	(mg/dL)	17.1	57	-	18	26.9	-	-
Cre	(mg/dL)	0.92	2.33	-	0.83	1.21	-	-
Na	(mEq/L)	141	135	-	138	137	-	-
K	(mEq/L)	4.5	4.4	-	3.8	3.9	-	-
Cl	(mEq/L)	106	98	-	101	98	-	-
CRP	(mg/dL)	0.98	10.73	-	-	12.7	-	-
CK	(IU/L)	229	-	-	-	-	-	-
NH3	(μg/dL)	-	107	-	-	-	14	-
ChE	(IU/L)	-	225	-	-	-	-	224
D-Bil	(mg/dL)	-	-	1.5	-	-	-	0.41
ANA		-	(-)	-	-	-	-	-

4 days after discontinuation
Type: DLST
Result: dabigatran etexilate methanesulfonate was positive.
Date unknown
Control :cpm:974
Dabigatran etexilate methanesulfonate : cpm: 2589,S.I(%): 265, Decision: positive
Disopyramide : cpm:1700,S.I(%): 174, Decision: negative
Furosemide : cpm: 1473,S.I(%): 151, Decision: negative
Day 5 of administration (day of discontinuation)
PT(INR):96.8(8.14)
19 days after discontinuation
PT(INR):12.6(1.04)
Date unknown
Anti-HBs:(-), Anti-HCV:(-)
Diagnostic imaging: Fatty liver and gallbladder wall thickening on abdominal ultrasonography and fatty liver and gallbladder wall edema/thickening on abdominal CT.

Suspected concomitant medications: disopyramide, furosemide, aspirin, levothyroxine sodium hydrate
Concomitant medication: allopurinol

3

Revision of Precautions (No. 288)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs in accordance with the Notifications dated September 12, 2017

1 Anticoagulants

Dabigatran etexilate methanesulfonate

Brand name	Prazaxa Capsules 75 mg, 110 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	Acute hepatic failure, hepatic function disorder, and jaundice: Acute hepatic failure, hepatic function disorder, and jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

2 Antivirals

Palivizumab (genetical recombination)

Brand name	Synagis Liquid 50 mg, 100 mg for Intramuscular Injection (AbbVie G.K.)
Adverse reactions (clinically significant adverse reactions)	Thrombocytopenia: Thrombocytopenia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

3 Biological preparations-Miscellaneous

Interferon beta

Brand name	Feron 1 million for injection, 3 million for injection, 6 million for injection (Toray Industries, Inc.)
Precautions concerning Dosage and Administration	The treatment duration should be carefully determined in consideration of the levels of clinical effects and adverse reactions. The usual adult dosage for intravenous administration or intravenous drip infusion is 6 million IU daily for one week, followed by 3 million IU daily, every day for five weeks, and 3 million IU daily, three times weekly from Week 7, and the treatment duration should be 34-36 weeks (total dose, 399 million IU).

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 new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing authorization holder (MAH) is responsible for collecting Adverse drug reaction (ADR) from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of August 31, 2017)
◎: Products for which EPPV was initiated after August 1, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Pralatrexate Difolta Injection 20 mg	Mundipharma K.K.	August 30, 2017
◎	Nusinersen Sodium Spinraza Intrathecal injection 12 mg	Biogen Japan Ltd.	August 30, 2017
◎	Leuprorelin Acetate[*1] Leuplin SR for Injection Kit 11.25 mg	Takeda Pharmaceutical Company Limited	August 25, 2017
◎	Eltrombopag Olamine[*2] Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	August 25, 2017
◎	Lyophilized Human Antithrombin III Concentrate[*3] Kenketu Nonthron 500 for Injection, 1500 for Injection	Nihon Pharmaceutical Co., Ltd.	August 25, 2017
◎	Florbetapir (^{18}F) Amyvid Injection	Fujifilm RI Pharma Co., Ltd.	August 21, 2017
	Clobetasol Propionate Comclo Shampoo 0.05%	Maruho Co., Ltd.	July 11, 2017
	Denosumab (Genetical Recombination) [*4] Pralia Subcutaneous Injection 60 mg Syringe	Daiichi Sankyo Company, Limited	July 3, 2017
	Fluvoxamine Maleate (1) Luvox Tablets 25 mg, 50 mg, 75 mg (2) Depromel Tablets 25 mg, 50 mg, 75 mg	(1) AbbVie GK (2) Meiji Seika Pharma Co., Ltd.	July 3, 2017
	Hydromorphone Hydrochloride Narurapid Tablets 1 mg, 2 mg, 4 mg, Narusus Tablets 2 mg, 6 mg, 12 mg, 24 mg	Daiichi Sankyo Propharma Co., Ltd.	June 19, 2017
	Naldemedine Tosilate Symproic Tablets 0.2 mg	Shionogi & Co., Ltd.	June 7, 2017
	Aflibercept Beta (Genetical Recombination) Zaltrap 100 mg I.V. Infusion, 200 mg I.V. Infusion	Sanofi K.K.	May 29, 2017
	Guanfacine Hydrochloride Intuniv Tablets 1 mg, 3 mg	Shionogi & Co., Ltd.	May 26, 2017
	Forodesine	Mundipharma K.K.	May 24, 2017

Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
Mundesine Capsule 100 mg		
Ixazomib Citrate Ninlaro capsules 2.3 mg, 3 mg, 4 mg	Takeda Pharmaceutical Company Limited	May 24, 2017
Ustekinumab (Genetical Recombination) *5 (1) Stelara Intravenous Infusion 130 mg, (2) Stelara Subcutaneous Injection 45 mg Syringe	Janssen Pharmaceutical K.K.	May 24, 2017
Drospirenone/Ethinylestradiol Betadex*6 YazFlex Combination Tablets	Bayer Yakuhin, Ltd.	April 21, 2017
Golimumab (Genetical Recombination)*7 Simponi Subcutaneous Injection 50 mg, 100 mg Syringe	Janssen Pharmaceutical K.K.	March 30, 2017
Zinc Acetate Dihydrate*8 Nobelzin Capsules 25 mg, 50 mg, Nobelzin Tablets 25 mg, 50 mg	Nobelpharma Co., Ltd.	March 24, 2017
Omalizumab (Genetical Recombination)*9 Xolair for S.C. Injection 75 mg, 150 mg	Novartis Pharma K.K.	March 24, 2017
Linaclotide Linzess Tablets 0.25 mg	Astellas Pharma Inc.	March 22, 2017
Artemether/Lumefantrine Riamet Combination Tablets	Novartis Pharma K.K.	March 7, 2017
Triamcinolone Acetonide MaQaid Intravitreal Injection 40 mg	Wakamoto Co., Ltd.	March 2, 2017
Choriogonadotropin Alfa (Genetical Recombination) Ovidrel Syringe 250 μg	Merck Serono Co., Ltd.	March 1, 2017
Apremilast Otezla Tablets 10 mg, 20 mg, 30 mg	Celgene K.K.	March 1, 2017

*1 Suppression of progression of congenital bulbospinal muscular atrophy

*2 Aplastic anaemia

*3 Portal vein thrombosis associated with decreased antithrombin III

*4 Suppression of progression of bone erosion associated with rheumatoid arthritis

*5 (1) Induction therapy for moderate to severe active crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments),
(2) maintenance therapy for moderate to severe active crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments)

*6 Improvement of pain in endometriosis, dysmenorrhoea

*7 Improvement and maintenance for moderate to severe ulcerative colitis (for use only in patients who have not sufficiently responded to conventional treatments)

*8 Hypozincemia

*9 Idiopathic chronic urticaria (limited to patients who are not adequately responsive to conventional treatments)