Pharmaceuticals and Medical Devices Safety Information

No. 286 December 2011

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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) website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

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Pharmaceuticals and Medical Devices Safety Information
No. 286 December 2011

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

[Outline of Information]

D: Distribution of Dear Healthcare Professional Letters *P*: Revision of Precautions *C*: Case Reports

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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

ADRs	Adverse drug reactions
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
CPAP	Continuous positive airway pressure
DIHS	Drug-induced hypersensitivity syndrome
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HHV-6	Human herpesvirus 6
MAH	Marketing authorization holder
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
γ-GTP	gamma-glutamyl transpeptidase

1

Cases of Non-payment under the Relief System for Sufferers from Adverse Drug Reactions and Proper Use of Drugs

1. Introduction

The Relief System for Sufferers from Adverse Drug Reactions 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 of drugs (including over-the-counter drugs), despite using them properly. This is a public relief service funded by contributions from marketing authorization holders of drugs as a way to fulfill some of their social responsibilities. As of the end of October 2011, approximately 9,000 persons (the actual number) have been granted relief benefits. Recently, the number of applications for the Relief System for Sufferers and payment of relief has been increasing (Table 1).

In 2004, the Relief System for Sufferers from Disease Infected from Biological Products, which is also public service, was established to bring prompt relief to people who suffered from adverse health effects such as disorders or disabilities caused by infections from virus, etc., despite using biological products properly. As of the end of March 2011, approximately 33 persons (the actual number) have been granted relief benefits.

People who have suffered from adverse health effects are encouraged to use the above services as much as possible; however, some cases of adverse health effects were not approved for relief benefits due to improper use of drugs, even though they were considered to be adverse drug reactions. Thus, MHLW/PMDA encourages healthcare professionals to promote proper use of drugs. This section presents the cases of non-payment of relief benefits.

Table 1 Number of relief benefits from the Relief Systems

Fiscal year	Number of applications	Number of payments	Number of non-payments
1980 to 1997	3,064 (2,506)	2,370 (1,971)	471 (345)
1998	361 (300)	306 (261)	49 (40)
1999	389 (318)	289 (238)	46 (41)
2000	480 (414)	343 (293)	61 (54)
2001	483 (411)	352 (294)	64 (54)
2002	629 (531)	352 (288)	79 (66)
2003	793 (702)	465 (407)	99 (82)
2004	769 (675)	513 (460)	119 (101)
2005	760 (643)	836 (745)	195 (157)
2006	788 (679)	676 (599)	169 (133)
2007	908 (785)	718 (617)	135 (107)
2008	926 (811)	782 (690)	136 (111)
2009	1,052 (947)	861 (776)	127 (96)
2010	1,018 (906)	897 (813)	122 (97)
Total	12,420 (10,628)	9,760 (8,452)	1,872 (1,484)

* The number of claimants (actual number)

- Number of claimants: a second claim for the same cause was counted.
- Actual number: a second claim for the same cause was not counted.
- The number of applications and the total number of payment and non-payment are not necessarily consistent since several months are required from the receipt of the application to the decision of benefit payment.

2. Information on the Relief Systems

For details of both Relief Systems, please refer to the PMDA website (http://www.pmda.go.jp/kenkouhigai.html) or the PMDSI No. 273 (October 2010) for outline of these services. The following materials are also available on the PMDA website (only available in Japanese language). Promotion of the Relief Systems using these materials is encouraged.

Relief System consultation services: 0120-149-931

- Relief System information booklet
  http://www.pmda.go.jp/kenkouhigai/file/higaikyusai.pdf (only available in Japanese language)
- Relief System information leaflet
  http://www.pmda.go.jp/kenkouhigai/ldp/file/fukusayo_leaflet.pdf (only available in Japanese language)
  http://www.pmda.go.jp/kenkouhigai/ldp/file/seibutuyurai.pdf (only available in Japanese language)
- Poster
  http://www.pmda.go.jp/kenkouhigai/file/kouhou_keiji.pdf (only available in Japanese language)
- Materials for medication bag
  http://www.pmda.go.jp/kenkouhigai/file/kouhou_kusuri.pdf (only available in Japanese language)

If any adverse health effect such as disorders or disabilities leading to hospital admission that are considered to be associated with a drug occurs despite proper use of the drug, healthcare professionals should provide information regarding the Relief Systems to the patient or bereaved families of the sufferers and help them file a benefit claim.

Caution should be paid to the cases not applicable for relief benefits as shown inTable 2.

Table 2 Examples of cases not applicable for 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 Preventive Vaccination Law). However, cases of adverse health effects resulting from voluntary vaccinations are applicable for under the Relief System for Sufferers.
b. Cases where it is clear who is responsible for adverse health effects, including the product liability of the marketing authorization holders of the drug or biological product.
c. Cases where it is necessary to use the drug or biological product 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.
d. Cases where it is not confirmed that the drug or biological product is used for a proper purpose and with a proper method.
   (e.g., cases where the drug or biological product has been used in ways other than indications approved by the Minister of Health, Labour and Welfare, or cases where the drug or biological product have not been used in accordance with the Precautions section in the package inserts)
e. Cases of adverse health effects caused by drugs inapplicable for the relief benefits[Note)]
   Note) Drugs inapplicable for the relief benefits:
   (i) Drugs used in the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (anticancer drugs, immunosuppressants, etc.)
   (ii) Drugs that do not have the possibility to cause adverse reactions, including drugs not used directly on human bodies or drugs without pharmacological effects (insecticides, antimicrobial agents, and in vitro diagnostics, etc.)
f. Cases of mild adverse health effects (including a case where hospital admission or treatment equivalent to inpatient care is not required) or cases where the disabilities caused by drugs fail to meet the disability

criteria defined under the Relief Systems[Note)]

Note) 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 his/her daily life performance (Grade 2)"

g. Cases where the deadline of claiming the relief benefits has passed.
h. Cases otherwise not approved by the Pharmaceutical Affairs and Food Sanitation Council of MHLW based on medical and pharmaceutical judgment
   - Cases where the disorders or disabilities are considered to be unlikely caused by adverse drug reactions (those are not considered to be associated with a drug)
   - Cases where it cannot be judged whether there are causalities or whether drugs are used for the proper purpose and with the proper method, because of insufficient documentation (impossible to judge)

3. Cases not applicable for relief benefits

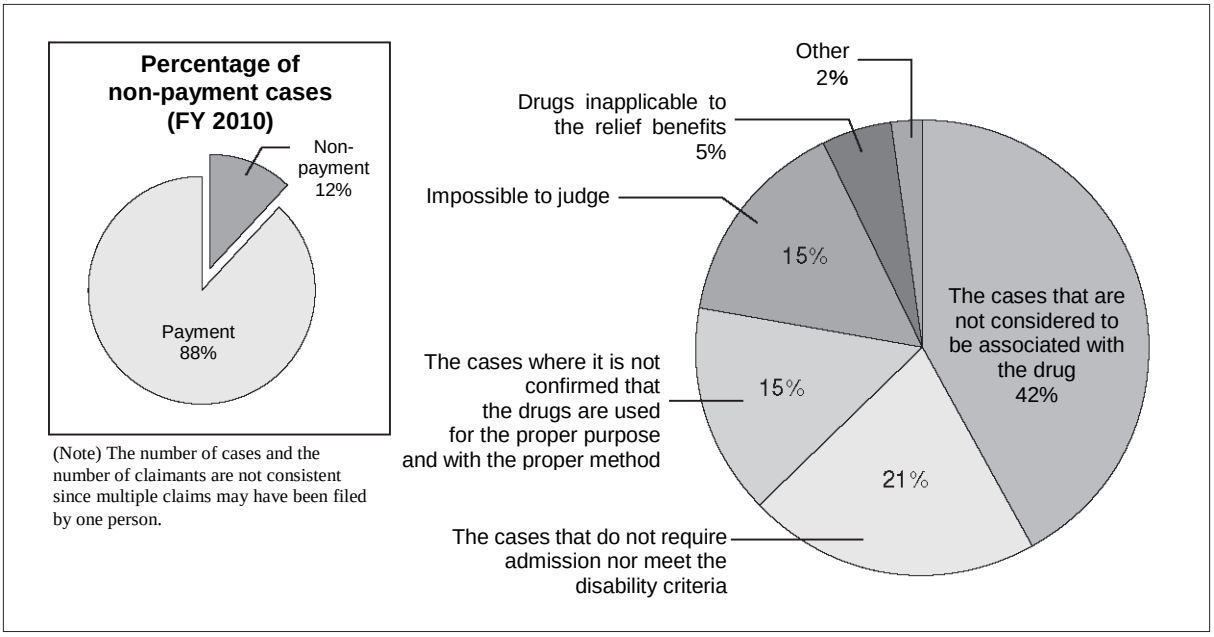
(1) Summary of cases of non-payment

As of the end of October 2011, approximately 9,000 persons have been granted relief benefits, while non-payment decisions were made for approximately 1,500 persons, under the Relief System for Sufferers from Adverse Drug Reactions. In FY2010, 813 persons were granted relief benefits while non-payment decisions were made for 97 persons.

The proportion of non-payment decision accounted for 12% of all claims. Reasons and details of non-payment are shown in Figure 1.

The most common reason for decision of non-payment was "The cases that are not considered to be associated with the drug," that is, cases where the causality between adverse health effects and the drugs is not confirmed, it accounted for 42%. Secondly, "The cases that do not require admission nor meet the disability criteria" accounted for 21%, followed by "The cases where it is not confirmed that the drugs are used for the proper purpose and with proper method" and "Impossible to judge" accounted for 15% each.

Figure 1 Reason for non-payment in FY 2010



(2) Example of cases where it is not confirmed that the drugs are used for the proper purpose and with the proper method

1) Cases where necessary tests are not performed

The following cases where necessary tests had not been performed were considered to be the cases where it is not confirmed that the drugs are used with the proper method. Healthcare professionals should pay attention to the "Precautions" section of the package insert to ensure proper use of drugs.

<Agranulocytosis associated with thiamazole>

Agranulocytosis occurred after approximately 2 months of treatment with oral thiamazole for hyperthyroidism. The blood test performed 1 month after administration, which showed no abnormality in white blood cell count or neutrophil count. However, no blood test had been performed in the following 4 weeks until agranulocytosis occurred.

The "Warnings" section of the package insert includes the following description: "Serious agranulocytosis has been reported especially within the first 2 months after administration, leading to fatal outcome in some cases. Blood tests including differential leukocyte count should be performed once every 2 weeks in principle for at least 2 months after administration, and periodically after that. If any abnormalities such as decreasing tendency of granulocytes are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken."

The PMDA has prepared information on proper use of drugs and alerted to healthcare professionals.
http://www.info.pmda.go.jp/iyaku_info/file/tekisei_pmda_05.pdf (only available in Japanese language)

<Fulminant hepatitis associated with benzbromarone>

Fulminant hepatitis occurred while using benzbromarone for the treatment of hyperuricaemia. No blood test had been performed during administration of benzbromarone (approximately 4 months).

The "Warnings" section of the package insert included the following description: "Serious hepatic disorders such as fulminant hepatitis have been reported especially within the first 6 months after administration, leading to serious outcomes such as death in some cases. Patients should be carefully monitored, including periodical liver function tests for at least the first 6 months after administration. If any abnormal liver function test results or jaundice are observed, administration of this drug should be discontinued, and appropriate measures should be taken." In November 2011, however, the revision of the package insert was made as follows to further alert healthcare professionals with regards to periodical liver function tests and subjective or objective symptoms. "Serious hepatic disorders such as fulminant hepatitis have been reported especially within the first 6 months after administration, leading to serious outcomes such as death in some cases. Liver function tests should be periodically performed for at least the first 6 months after administration. Patients should be carefully monitored, and if any abnormal liver function test results or jaundice are observed, administration of this drug should be discontinued, and appropriate measures should be taken."

The PMDA has prepared information on proper use of drugs and alerted to healthcare professionals.
http://www.info.pmda.go.jp/iyaku_info/file/tekisei_pmda_04.pdf (only available in Japanese language)
http://www.pmda.go.jp/english/service/pdf/request/No4.pdf (in English)

<Agranulocytosis associated with salazosulfapyridine>

Agranulocytosis occurred during the treatment with salazosulfapyridine enteric tablets for rheumatoid arthritis. No test had been performed for approximately 5 weeks after starting administration of salazosulfapyridine enteric tablets.

The "Important Precautions" section of the package insert includes the following description: "Patients should be carefully monitored for changes in their clinical symptoms during treatment with this drug and periodic haematological and liver function tests should be performed (once every 2 weeks in the first 3 months, once every 4 weeks in the next 3 months, and once every 3 months after 6 months of administration in principle)."

The PMDA has prepared information on proper use of drugs and alerted to healthcare professionals.
http://www.info.pmda.go.jp/iyaku_info/file/tekisei_pmda_01.pdf (only available in Japanese language)
http://www.pmda.go.jp/english/service/pdf/request/No1.pdf (in English)

2) Cases where the drugs were used in ways other than approved indications, dosage and administration

The following case where the drug was used in ways other than approved indication and dosage and administration was also considered to be the case where it is not confirmed that the drugs are used for the proper purpose and with the proper method.

<Pseudoaldosteronism associated with monoammonium glycyrrhizinate/glycine/

L-cysteine hydrochloride hydrate>

The patient was diagnosed with multiple alopecia areata and monoammonium glycyrrhizinate/ glycine/L-cysteine hydrochloride hydrate and other drugs were used. Gait disorder gradually appeared, and the patient was diagnosed with pseudoaldosteronism and hospitalized for 2 weeks. In this case, monoammonium glycyrrhizinate/glycine/L-cysteine hydrochloride hydrate was used for the treatment of alopecia areata, which is not included in the indications in the package insert.

The "Indications" section of the package insert includes "eczema/dermatitis, urticaria, cutaneous pruritus, drug eruption/toxicoderma, stomatitis, infant strophulus, and phlyctenules" and "improvement of liver dysfunction in chronic liver disease."

3) Cases where the drugs are used in noncompliance with Precautions

The following cases where the drugs were used in noncompliance with "Contraindications" or "Important Precautions" in the "Precautions" section were also considered to be the cases where it is not confirmed that the drugs are used for the proper purpose and with the proper method.

<Skin ulcer associated with lidocaine hydrochloride/adrenaline injection>

The patient visited a hospital with a pain of corn in the right fourth toe. Lidocaine hydrochloride/adrenaline injection was locally administered to the toe, and the corn was removed with tweezers. The use of lidocaine/adrenaline injection in toes is contraindicated. Next day the pain intensified, and the patient was diagnosed with a skin ulcer in the right fourth toe.

The "Contraindications" section of the package insert includes the following description: "[Conduction or infiltration anesthesia] Anesthesia in ears, fingers, toes or penis [necrosis may occur]."

<Generalised drug eruption associated with amoxicillin>

Generalised drug eruption occurred after administration of oral amoxicillin for the treatment of acute pharyngitis. Amoxicillin was prescribed despite the patient had a history of rash associated with penicillin.

The "Relative Contraindications" section of the package insert includes the following description: "Patients with a history of hypersensitivity to ingredients of this drug or penicillin antibiotics"

4) Cases where patients take the drugs by self-judgment

The following cases where an ethical drug prescribed by a physician was used based on the patient's self-judgment and where an ethical drug prescribed to a family member was used were also considered to be the cases where it is not confirmed that the drugs are used for the proper purpose and with the proper method.

<Drug-induced hypersensitivity syndrome (DIHS) associated with carbamazepine>

The patient visited a hospital with chief complaint of right facial pain and was diagnosed with trigeminal neuralgia. DIHS occurred during the treatment with carbamazepine. The physician instructed the patient to discontinue carbamazepine due to an adverse reaction, but the patient continued to use the drug based on self-judgment because of unbearable pain or other reasons.

<Drug-induced hepatic disorder associated with common cold drug>

The patient had cold symptoms and took an ethical common cold drug that had been prescribed to another family member. Hepatic dysfunction and jaundice occurred subsequently. In this case, the patient used the drug prescribed to another person based on self-judgment.

4. Closing comments

Healthcare professionals are encouraged to thoroughly read the "Precautions" section of the package insert before using drugs and to use them properly. Please note that the cases where drugs are not used properly are not applicable for the relief benefits under public relief systems, even though the adverse health effects are suspected to have been caused by adverse drug reactions.

As mentioned in Section 2, when adverse reactions occur and healthcare professionals are

consulted by their patient about the reactions, the healthcare professionals should provide information regarding the Relief Systems to the patient, if the reactions are possibly applicable for the relief benefits. MHLW/PMDA hopes for your particular cooperation in preparing the documents required to claim these relief benefits.

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated November 29, 2011, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Epoprostenol Sodium

Brand Name (name of company)	Flolan for injection 0.5 mg, 0.5 mg (GlaxoSmithKline K.K.) EPOPROSTENOL for Intravenous Injection 0.5 mg "Taiyo", 1.5 mg "Taiyo" (Taiyo Pharmaceutical Industry Co., Ltd.)
Therapeutic Category	Cardiovascular agents-Miscellaneous
Indications	Pulmonary arterial hypertension

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Hyperthyroidism may occur. Patients should be carefully monitored including periodic tests. If any abnormalities are observed, 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) for the past 3 years (April 1, 2008 to September 5, 2011)

- Hyperthyroidism: 5 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 450 (2011)

Launched in Japan: April 1999 (Flolan for injection 0.5 mg)
July 2001 (Flolan for injection 1.5 mg)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 10s	Pulmonary arterial hypertension	5 ng/kg/min for 36 days 6 ng/kg/min for 26 days	**Pain in jaw, epistaxis, autoimmune hyperthyroidism** Day 15 of administration: The patient developed pain in her jaw. No therapeutic measures were taken and clinical course was followed with self-control. Day 100 of administration: Epistaxis developed. Epistaxis occurred about 2-3 times/month. Clinical course was followed without therapeutic measures.

			7 ng/kg/min for 28 days 14.6 ng/kg/min for 32 days 9 ng/kg/min for 28 days 10 ng/kg/min for 17 days 11 ng/kg/min for 39 days 12 ng/kg/min for 35 days 13 ng/kg/min for 45 days 15 ng/kg/min for 68 days 16 ng/kg/min for unknown duration 22 ng/kg/min for unknown duration 20.4 ng/kg/min for unknown duration 20.3 ng/kg/min for unknown duration	1 year and 11 months after administration: Autoimmune hyperthyroidism developed. Abnormalities such as Triiodothyronine (T_3) 5.7 ng/dL, Thyroxine (T_4) 2.5 μg/dL, and Thyroid-stimulating hormone (TSH) ≤ 0.01 were observed.. Day 746 of administration: Under hospitalization, thyroglobulin antibody level was ≥ 5600 and microsome antibody level was ≥ 25600, and thus the patient was diagnosed with autoimmune hyperthyroidism. Administration of thiamazole was started. Day 833 of administration: T_3, T_4, and TSH improved to 3.6 ng/dL, 1.4 μg/dL, and 7.31, respectively.
	Concomitant medications: furosemide, spironolactone, warfarin potassium, potassium chloride, dextromethorphan hydrobromide, ferrous sulfate, ascorbic acid/calcium pantothenate, potassium gluconate, fluticasone propionate, sulbactam sodium/ampicillin sodium, meropenem hydrate, ursodeoxycholic acid, ambroxol hydrochloride, thiamazole			

Laboratory Examination

	1 year and 11 months after administration	Day 746 of administration	Day 833 of administration
T_3 (ng/dL)	5.7	—	3.6
T_4 (μg/dL)	2.5	—	1.4
TSH	≤ 0.01	—	7.31
Thyroglobulin antibody	—	≥ 5600	—
Microsome antibody	—	≥ 25600	—

3

Revision of Precautions (No. 232)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated November 29, 2011 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 Urogenital and anal organ agents-Miscellaneous

Solifenacin Succinate

Brand Name

Vesicare Tablets 2.5 mg, 5 mg, Vesicare OD Tablets 2.5 mg, 5 mg
(Astellas Pharma Inc.)

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored, and if abnormalities including urticaria, dyspnoea or decreased blood pressure are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Paralytic ileus: Paralytic ileus may occur. Patients should be carefully monitored, and if severe constipation, abdominal distension, etc. are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Hallucination, delirium: Hallucination, delirium may occur. Patients should be carefully monitored and if these symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

2 Hypnotics and sedatives, anxiolytics

Nitrazepam

Brand Name

NELBON TABLETS 5 mg, 10 mg, NELBON POWDER 1%
(Daiichi Sankyo Company, Limited),
Benzalin Tablet 2, 5, 10, Benzalin Fine Granule 1% (Shionogi & Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Hepatic dysfunction, jaundice: Hepatic dysfunction with elevated AST (GOT), ALT (GPT), and γ-GTP or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

3 Otological agents

Fluticasone Furoate

Brand Name

Allermist 27.5 μg 56 metered Nasal Spray (GlaxoSmithKline K.K.)

Important Precautions

Systemic effects including Cushing's syndrome, Cushingoid symptom, suppression of adrenocortical function, growth retardation in children, decreased bone density, cataract and glaucoma may occur with use of nasal corticosteroids, although the possibility is low in comparison to systemic corticosteroids. Periodic examinations should be performed especially when this drug is administered long-term at a high dose. If systemic effects are observed, appropriate measures should be taken.

4 Otological agents

Fluticasone Propionate (nasal solution)

Brand Name

Flunase Nasal Solution 50 μg 28 metered sprays, Flunase Nasal Solution 50 μg 56 metered sprays, Flunase Nasal Solution 25 μg 56 metered sprays for Pediatric (GlaxoSmithKline K.K.)

Important Precautions

Systemic effects including Cushing's syndrome, Cushingoid symptom, suppression of adrenocortical function, growth retardation in children, decreased bone density, cataract and glaucoma may occur with use of nasal corticosteroids, although the possibility is low in comparison to systemic corticosteroids. Periodic examinations should be performed especially when this drug is administered long-term at a high dose. If systemic effects are observed, appropriate measures should be taken.

5 Diuretics

Acetazolamide
Acetazolamide Sodium

Brand Name

DIAMOX Pow. DIAMOX Tab. 250 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
DIAMOX for Inj. 500 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Metabolic acidosis, electrolyte abnormality: Metabolic acidosis or electrolyte abnormality such as hypokalaemia and hyponatraemia may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

6 Antituberculosis

Isoniazid

Brand Name

ISCOTIN POWDER, ISCOTIN TABLETS 100 mg, ISCOTIN INJECTION 100 mg (Daiichi Sankyo Company, Limited),
HYDRA TABLET [OTSUKA] 50 mg (Otsuka Pharmaceutical Factory, Inc.)

Adverse Reactions (clinically significant adverse reactions)

Drug-induced hypersensitivity syndrome:
(Initial symptoms: rash, pyrexia)
(Secondary findings: hepatic dysfunction, swollen lymph nodes, increased white blood cells, eosinophilia, atypical lymphocytes, etc.)
.Drug-induced hypersensitivity syndrome may occur, frequently with the reactivation of viruses including human herpes virus 6 (HHV-6). Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised.

Reference Information

Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions: Drug-Induced Hypersensitivity Syndrome

7 Antituberculosis

Isoniazid Sodium Methanesulfonate Hydrate

Brand Name

NEOISCOTIN POWDER, NEOISCOTIN TABLETS 100 mg
(Daiichi Sankyo Company, Limited)

Clinically significant adverse reactions (Isoniazid)	**Drug-induced hypersensitivity syndrome:** (Initial symptoms: rash, pyrexia) (Secondary findings: hepatic dysfunction, swollen lymph nodes, increased white blood cells, eosinophilia, atypical lymphocytes, etc.) Drug-induced hypersensitivity syndrome may occur, frequently with the reactivation of viruses including human herpes virus 6 (HHV-6). Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised.
Reference Information	Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions: Drug-Induced Hypersensitivity Syndrome

8 Synthetic narcotics

Remifentanil Hydrochloride

Brand Name	Ultiva Intravenous 2 mg, 5 mg (Janssen Pharmaceutical K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Generalised convulsion**: Generalised convulsion may occur. Patients should be carefully monitored, and appropriate measures should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for 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 is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for taking safety measures. The aim of the EPPV is to promote the rational proper use of the drug in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of December 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Pioglitazone Hydrochloride/Glimepiride SONIAS Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	June 6, 2011
Memantine Hydrochloride MEMARY TABLETS 5 mg, 10 mg, 20 mg	Daiichi Sankyo Company, Limited	June 8, 2011
Adalimumab (Genetical Recombination) HUMIRA for s.c. injection syringe 40 mg/0.8 mL, HUMIRA for s.c. injection syringe 20 mg/0.4 mL*1	Abbott Japan Co., Ltd.	July 1, 2011
Erlotinib Hydrochloride TARCEVA Tablets 25 mg, 100 mg*2	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Gabapentin GABAPEN Tablets 200 mg, 300 mg, 400 mg*3	Pfizer Japan Inc.	July 1, 2011
Peginterferon Alfa-2a (Genetical Recombination) PEGASYS s.c. 90 μg, 180 μg	Chugai Pharmaceutical Co., Ltd.	July 1, 2011*4 September 26, 2011*5
Lamotrigine Lamictal Tablets 25 mg, 100 mg*6	GlaxoSmithKline K.K.	July 1, 2011
Ribavirin COPEGUS Tablet 200 mg*7	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Edoxaban Tosilate Hydrate LIXIANA TABLETS 15 mg, 30 mg	Daiichi Sankyo Company, Limited	July 19, 2011
Eribulin Mesilate Halaven injection 1 mg	Eisai Co., Ltd.	July 19, 2011
Tramadol Hydrochloride/Acetaminophen TRAMCET Combination Tablets	Janssen Pharmaceutical K.K.	July 19, 2011
Rivastigmine EXELON PATCH 4.5 mg, 9 mg, 13.5 mg, 18 mg	Novartis Pharma K.K.	July 19, 2011
Rivastigmine RIVASTACH Patch 4.5 mg, 9 mg, 13.5 mg, 18 mg	Ono Pharmaceutical Co., Ltd.	July 19, 2011
Epoetin Beta Pegol (Genetical Recombination) MIRCERA Injection Syringe 25 μg, 50 μg, 75 μg, 100 μg, 150 μg, 200 μg, 250 μg	Chugai Pharmaceutical Co., Ltd.	July 20, 2011

Pramipexole Hydrochloride Hydrate Mirapex-LA Tablets 0.375 mg, 1.5 mg	Nippon Boehringer Ingelheim Co., Ltd.	July 20, 2011
Mitiglinide Calcium Hydrate/Voglibose GLUBES Combination Tab.	Kissei Pharmaceutical Co., Ltd.	July 22, 2011
Desflurane Suprane Inhalational Anesthetic Solution	Baxter Limited	July 29, 2011
Buprenorphine NORSPAN TAPE 5 mg, 10 mg, 20 mg	Mundipharma K.K.	August 4, 2011
Escitalopram Oxalate LEXAPRO Tab. 10mg	Mochida Pharmaceutical Co., Ltd.	August 22, 2011
Recombinant Adsorbed Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine (Yeast Origin) GARDASIL Aqueous Suspension for Intramuscular Injection, GARDASIL Aqueous Suspension for Intramuscular Injection Syringe	MSD K.K.	August 26, 2011
Pancrelipase LipaCreon Granules 300 mg Sachet, LipaCreon Capsules 150 mg	Abbott Japan Co., Ltd.	August 30, 2011
Levobupivacaine Hydrochloride POPSCAINE 0.5% inj. 50 mg/10 mL, POPSCAINE 0.5% inj. syringe 50 mg/10 mL	Maruishi Pharmaceutical Co., Ltd.	September 7, 2011
Vorinostat ZOLINZA Capsules 100 mg	MSD K.K.	September 14, 2011
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg	AstraZeneca K.K.	September 15, 2011
Landiolol Hydrochloride COREBETA for Intravenous 12.5 mg	Ono Pharmaceutical Co., Ltd.	September 15, 2011
Linagliptin Trazenta Tablets 5 mg	Nippon Boehringer Ingelheim Co., Ltd.	September 15, 2011
Golimumab (Genetical Recombination) Simponi Subcutaneous Injection Syringe 50 mg	Janssen Pharmaceutical K.K.	September 16, 2011
Minodronic Acid Hydrate Bonoteo Tablets 50 mg	Astellas Pharma Inc.	September 16, 2011
Minodronic Acid Hydrate RECALBON Tablets 50 mg	Ono Pharmaceutical Co., Ltd.	September 16, 2011
Mirabegron Betanis Tablets 25 mg, 50 mg	Astellas Pharma Inc.	September 16, 2011
Alogliptin Benzoate/Pioglitazone Hydrochloride LIOVEL Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	September 20, 2011
Indacaterol Maleate onbrez inhalation capsules 150 μg	Novartis Pharma K.K.	September 20, 2011
Daptomycin CUBICIN IV 350 mg	MSD K.K.	September 22, 2011
Itraconazole ITRIZOLE Oral Solution 1%*[8]	Janssen Pharmaceutical K.K.	September 26, 2011
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*[9]	Chugai Pharmaceutical Co., Ltd.	September 26, 2011

Olopatadine Hydrochloride ALLELOCK Granules 0.5%*10	Kyowa Hakko Kirin Co., Ltd.	November 15, 2011
Live Attenuated Human Rotavirus Vaccine, Oral Rotarix Oral Solution	GlaxoSmithKline K.K.	November 21, 2011
Imiquimod BESELNA CREAM 5%*11	Mochida Pharmaceutical Co., Ltd.	November 25, 2011
Teriparatide Acetate Teribone Inj. 56.5 μg	Asahi Kasei Pharma Corporation	November 25, 2011
Fulvestrant FASLODEX intramuscular injection 250 mg	AstraZeneca K.K.	November 25, 2011
Modafinil MODIODAL Tablets 100 mg*12	Alfresa Pharma Corporation	November 25, 2011
Telaprevir TELAVIC Tablets 250 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride IMUSERA Capsules 0.5 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride GILENYA Capsules 0.5 mg	Novartis Pharma K.K.	November 28, 2011

*1 An additional indication for "treatment of patients with active polyarticular juvenile idiopathic arthritis"

*2 An additional indication for "treatment of patients with non-resectable pancreatic carcinoma"

*3 An additional administration for "pediatrics"

*4 An additional indication for "improvement of viraemia in compensated cirrhosis C in combination therapy with ribavirin"

*5 An additional indication for "improvement of viraemia in chronic active hepatitis B

*6 An additional indication for "suppression of recurrent/relapsed mood episodes in patients with bipolar disorder"

*7 An additional indication for "improvement of viraemia in compensated cirrhosis C in combination therapy with peginterferon alfa-2a (genetical recombination)"

*8 Additional indications for "treatment of patients with fungal infection caused by *Aspergillus*, *Cryptococcus*, *Blastomyces*, or *Histoplasma* (fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, blastomycosis, histoplasmosis)", "treatment of patients with febrile neutropenia of suspected fungal infection", and "prophylaxis of deep mycosis in patients with haematological malignancy possibly associated with neutropenia or patients who underwent hematopoietic stem cell transplantation"

*9 An additional indication for "treatment of patients with inoperable or recurrent breast cancer"

*10 An additional administration for "pediatrics (aged 2 to under age of 7)"

*11 An additional indication for "treatment of patients with actinic keratosis (limited to face or baldness)"

*12 An additional indication for "treatment of excessive daytime sleepiness in patients with obstructive sleep apnoea syndrome who receive the treatment of airway obstruction with continuous positive airway pressure (CPAP) therapy, etc."