Pharmaceuticals and Medical Devices Safety Information

No. 276 January 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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Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

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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No. 276 January 2011

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

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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

ADR	Adverse drug reaction
CT	Computed tomography
CK (CPK)	Creatine kinase (Creatine phosphokinase)
EPPV	Early Post-marketing Phase Vigilance
EMA	European Medicines Agency
FY	Fiscal year
FDA	Food and Drug Administration
MAH	Marketing authorization holder
MHRA	Medicines and Healthcare products Regulatory Agency
OTC	Over-the-counter drug
PL	Package Leaflet
SPC	Summary of Product Characteristics
UK	United Kingdom
US	United States

1

Safety Measures Against Photosensitivity Due to Topical Ketoprofen

[Brand Name]: Major product names are showed .

	Active ingredient	Brand Name (name of company)
Active ingredient Brand Name (name of company)	[1][2][3] Ketoprofen (cream, gel, lotion, tape, and poultice) [4] Over-the-counter drug: medical products containing ketoprofen (dermatologic preparation)	[1] EPATEC GEL 3%, EPATEC CREAM 3%, EPATEC LOTION 3% (Zeria Pharmaceutical Co., Ltd.) [2] MOHRUS TAPE 20 mg, MOHRUS TAPE L 40 mg (Hisamitsu Pharmaceutical Co., Inc.) [3] KETOTAX TAPE, KETOTAX TAPE L (Toko Pharmaceutical Industrial Co., Ltd.) [4] Epasgel (Takaichi Pharmaceutical Industry)
Therapeutic Category	Analgesics, anti-itchings, astringents, anti-inflammatory agents	
Indications	[1] Relief of pain and inflammation associated with the following disorders and symptoms Osteoarthritis, scapulohumeral periarthritis, tendonitis and tenosynovitis, peritendinitis, humeral epicondylitis (e.g. tennis elbow), myalgia, post-traumatic swelling and pain [2] Relief of pain and inflammation associated with chronic symptoms (blood flow disorder, muscle spasms, muscle contracture) in the following disorders Lumbago (myofascial lumbago, spinal osteoarthritis, discopathy, lumbar sprain), osteoarthritis, scapulohumeral periarthritis, tendonitis and tenosynovitis, peritendinitis, humeral epicondylitis (e.g. tennis elbow) Relief of local joint pain in rheumatoid arthritis [3] Relief of pain and inflammation associated with the chronic symptoms (blood flow disorder, muscle spasms, muscle contracture) in the following disorders Lumbago (myofascial lumbago, spinal osteoarthritis, discopathy, lumbar sprain), osteoarthritis, scapulohumeral periarthritis, tendonitis and tenosynovitis, peritendinitis, humeral epicondylitis (e.g. tennis elbow) [4] Myalgia, lower back pain, arthralgia, tenosynovitis (hand or wrist pain), bruise, sprain, elbow pain (e.g. tennis elbow), shoulder pain associated with shoulder muscle stiffness	

1. Introduction

Topical ketoprofen, a percutaneous anti-inflammatory analgesic, is currently available as an ethical drug in Japan in the following dosage forms: gel, poultice, lotion, cream, and tape approved in July 1986, March 1988, September 1988, March 1989, and August 1995, respectively (the FY 2009 amount of shipment was approx. 7,500 kg of gel, approx. 660 million poultices, approx. 74,000 kg of lotion, approx. 16,000 kg of cream, and approx. 2.4 billion pieces of tape). On the other hand, ketoprofen gel, lotion, and cream were also approved as over-the-counter (OTC) drugs in December 1994, and ketoprofen poultices in August 2005 (the FY 2009 shipment was approx. 160 kg of gel, approx. 480 kg of lotion, approx. 160 kg of cream, and approx. 1.4 million poultices).

Regarding possible photosensitivity due to topical ketoprofen, alerts against systemic photosensitivity due to exposure to ultraviolet light were included to the package inserts of all ketoprofen, whether ethical or OTC drugs, in December 2001 based on the case series in Japan.[1)]

Based on the study report on the cross-sensitization to ketoprofen published in January 2003, alerts against the cross-sensitive components to ketoprofen were added to the package inserts.[2,3)]

Topical ketoprofen is also distributed as a percutaneous anti-inflammatory analgesic in Europe. The European Medicines Agency (EMA) issued a press release in July 2010, based on its review of the efficacy and safety of the drug by the Committee for Medicinal Products for Human Use (CHMP), that alerts against possible photosensitivity due to prescription ketoprofen should be strengthened and that ketoprofen should no longer be available over the counter.[4)]

In light of these circumstances, the MHLW conducted an investigation and an expert review at the Subcommittee on Drug Safety Committee on Drug Safety Pharmaceutical Affairs and Food Sanitation Council, on October 8, 2010, to take further safety measures against possible photosensitivity due to topical ketoprofen.[5)] As for OTC topical ketoprofen, ketoprofen poultices have been marketed as first-class OTC drugs, while ketoprofen gel, lotion, and cream have been marketed as second-class OTC drugs. However, the risk categories of OTC topical ketoprofen were also reviewed based on the discussion on further safety measures and the results of post-marketing surveillance on ketoprofen poultices. Details are described below.

2. Photosensitivity due to topical ketoprofen

(1) The situation in Europe

Following a review of the efficacy and safety of topical ketoprofen, the EMA concluded that the risk of serious photosensitivity was low (0.6 to 12.4 per 1,000,000 persons according to the estimate of a manufactuer), and that the benefit of topical ketoprofen outweighed its risk if the drug was used properly. However, the EMA concluded that the following safety measures should be taken; because (1) photosensitivity associated with ketoprofen were noted and some cases may be serious, (2) photosensitivity due to co-sensitization to ketoprofen and octocrylene (a chemical compound widely used as a sun filter in cosmetic products) has been reported, and (3) ketoprofen should be properly used to minimize the risk of photosensitivity.[4)]

- Contraindications in patients with a history of photosensitivity or skin allergy to sunscreen or perfume should be included in the sections of "Contraindications," "Special warnings and special precautions for use," and "Undesirable effects" of the Summary of Product Characteristics (SPC) and Package Leaflet (PL) of ketoprofen marketed in Europe, as well as an alert against possible adverse skin reactions when used together with octocrylene-containing products.
- An alert against possible photosensitivity should be provided in a pictogram and texts on the packages.
- Information on the risk of photosensitivity should be communicated to healthcare providers and patients.
- Topical ketoprofen should no longer be available over the counter.

(2) Adverse reaction reports and further safety measures in Japan

Based on the accumulated adverse reaction reports on serious photosensitivity due to topical ketoprofen, alerts against serious systemic photosensitivity were added to the sections of "Precautions of Indications," "Important Precautions" and "Clinically Significant Adverse Reactions" in the package insert in 2001.[1)] In 2003, an alert against the use of ketoprofen in patients with a history of hypersensitivity to the cross-sensitive components to ketoprofen (tiaprofenic acid, suprofen, fenofibrate and oxybenzone) was added to the section of "Contraindications" based on the report on the cross-sensitization to ketoprofen.[2,3)]

From the initial launches of topical ketoprofen (ethical drugs) in 1986 to May 2010, 4,252 cases of skin disorders were reported (including 90 serious cases) as adverse reactions and 2,028 of them were photosensitivity (including 47 serious cases). **Table 1** presents the number of cases of photosensitivity according to the ketoprofen dosage form.

Table 1 Photosensitivity reported as adverse reactions to topical ketoprofen (ethical drugs)

Dosage form	Number of cases	Number of serious cases	Proportion of serious cases (%)
Poultice	205	8	3.9
Tape	1,770	37	2.1
Gel	23	0	0
Lotion	22	1	4.5
Cream/ointment	8	1	12.5
Total	2,028	47	2.3

Incidence of photosensitivity in patients receiving prescriptions of topical ketoprofen was compared with that of other anti-inflammatory analgesics (flurbiprofen, indometacin, or felbinac) between January 2005 and December 2008 using data from the health insurance societies' claims data provided by Japan Medical Data Center Co., Ltd. Photosensitivity was diagnosed within 2 months of prescription in 0.05% (35/65,897) of patients using topical ketoprofen, 0.03% (10/32,893) of those using topical flurbiprofen, 0.05% (11/20,338) of those using topical indometacin and 0.02% (11/50,975) of those using topical felbinac. The proportion of patients who experienced photosensitivity after using topical ketoprofen was slightly higher or equivalent to those using other anti-inflammatory analgesics, with no substantial difference in incidence of photosensitivity.

From the initial launches in 1997 to June 2010, 538 cases of skin disorders (including 2 serious cases) were reported as an adverse reaction associated with OTC topical ketoprofen, and 28 of them (including 2 serious cases) were photosensitivity.

Therefore, the incidence of photosensitivity due to ethical topical ketoprofen in Japan is comparable to that of other anti-inflammatory analgesics. The proportion of serious cases seems to be smaller than that in Europe. However, the MHLW concluded that the appropriate alerts, in accordance with those in Europe, are necessary based on the expert review since a certain number of cases of photosensitivity are reported in Japan every year.

On the other hand, the MHLW considered that discontinuation of OTC topical ketoprofen would be unnecessary at the moment based on the small number of reports on photosensitivity as an adverse reaction. However, the MHLW concluded that an alert against possible photosensitivity due to OTC ketoprofen should be issued as well. Further, MHLW recommended that an alert against concomitant use of ketoprofen with an octocrylene-containing product should be issued as preventive measures.

Based on the above, the MHLW required MAHs of ketoprofen (both ethical and OTC drugs) to revise Precautions in the package insert on October 12, 2010.

In addition, the following measures are required to be taken to alert distributors and consumers against possible photosensitivity due to OTC ketoprofen in an easy-to-understand manner.

1. to provide distributors with information on the revision of Precautions.
2. to change the size and location of the pictogram on the product packaging and labeling
3. to provide consumers with information using materials to alert them against possible photosensitivity.

Since photosensitivity may occur several days or months after using topical ketoprofen, caution should be taken for a while after using the drug. The product package of ketoprofen, both ethical and OTC drugs, already included an alert to avoid exposing the treated area to ultraviolet light for 2 weeks after using ketoprofen gel, lotion, or cream and for 4 weeks after using ketoprofen poultices. The MHLW required that the product package now be revised to avoid exposure for 4 weeks after using ketoprofen gel, lotion, or cream as well.

3. Review of risk classification of OTC topical ketoprofen

According to the risk classification of OTC topical ketoprofen, ketoprofen poultice, which had been under the post-marketing surveillance, was classified as a first-class OTC drug and other dosage forms (e.g., gel and cream) as a second-class OTC drug. Following submission of the post-marketing surveillance report of ketoprofen poultices and the review of safety measures against possible photosensitivity due to ketoprofen in the context of the regulatory actions taken in Europe, the risk classification of OTC topical ketoprofen was also reviewed.

The MHLW concluded that, based on the review, all OTC topical ketoprofen did not need to be re-classified as a first-class OTC drug, but a pharmacist or a registered salesperson should provide information in person about topical ketoprofen including gel and cream as with ketoprofen poultices. Since thorough, easy-to-understand information should be provided to customers concerning photosensitivity, the MHLW concluded topical ketoprofen including gel and cream should be classified as designated second-class OTC drugs, which are designated by the Minister of Health, Labour and Welfare as those requiring special attention. These medicines should be displayed within 7 meters from the facilities for providing information.

4. Closing comments

Topical ketoprofen, available as an ethical drug or an OTC drug, is widely used as an anti-inflammatory analgesic. Information on the potential risk of photosensitivity needs to be provided thoroughly to not only healthcare providers, but also patients and consumers through easy-to-understand alerts against possible photosensitivity by improving product packaging and labeling and distributing materials to patients.

Healthcare providers are encouraged to provide information to patients and consumers using package labels and special materials, to continue to monitor possible photosensitivity due to topical ketoprofen, and to report immediately any adverse reactions. Especially, pharmacists or registered salespersons should handle strictly OTC topical ketoprofen as designated a second-class OTC drug and provide proactively information on the risks of photosensitivity to consumers.

Specific revisions of the Precautions in the package insert of ketoprofen products are listed below. (The underlined parts are revised.)

Ketoprofen (cream)

[Contraindications]	Patients with a history of hypersensitivity to products containing tiaprofenic acid, suprofen, fenofibrate, oxybenzone, or <u>octocrylene (e.g., sunscreen, perfume)</u> <u>Patients with a history of photosensitivity</u>
[Important Precautions]	Photosensitivity may occur. Patients should avoid outdoor activities regardless of the weather while using this drug. The application site of this drug should be protected from sunlight with clothes or a protector when going outside. White or sheer clothes may let in ultraviolet light. Patients should wear colored clothes that let in only small amounts of ultraviolet light. Since photosensitivity may occur several days or months after using the drug, the same caution should be taken for a while after use. <u>If any abnormalities are observed, this drug should be discontinued immediately, treated areas should be protected from sunlight and appropriate measures should be taken.</u> <u>Patients should also wash their hands carefully after using this drug.</u>
[Precautions concerning Use]	<u>Patients should wash their hands carefully after using this drug.</u>

Ketoprofen (gel, lotion)

[Contraindications]	Patients with a history of hypersensitivity to products containing tiaprofenic acid, suprofen, fenofibrate, oxybenzone, or octocrylene (e.g., sunscreen, perfume) Patients with a history of photosensitivity
[Important Precautions]	Photosensitivity may occur. Patients should avoid outdoor activities regardless of the weather while using this drug. The application site of this drug should be protected from sunlight with clothes or a protector when going outside. White or sheer clothes may let in ultraviolet light. Patients should wear colored clothes that let in only small amounts of ultraviolet light. Since photosensitivity may occur several days or months after using the drug, the same caution should be taken for a while after use. If any abnormalities are observed, this drug should be discontinued immediately, treated areas should be protected from sunlight and appropriate measures should be taken. Patients should also wash their hands carefully after using this drug.
[Precautions concerning Use]	Patients should wash their hands carefully after using this drug.

Ketoprofen (tape, poultice)

[Contraindications]	Patients with a history of hypersensitivity to products containing tiaprofenic acid, suprofen, fenofibrate, oxybenzone, or octocrylene (e.g., sunscreen, perfume) Patients with a history of photosensitivity
[Important Precautions]	Photosensitivity may occur. Patients should avoid outdoor activities regardless of the weather while using this drug. The application site of this drug should be protected from sunlight with clothes or a protector when going outside. White or sheer clothes may let in ultraviolet light. Patients should wear colored clothes that let in only small amounts of ultraviolet light. Since photosensitivity may occur several days or months after using the drug, the same caution should be taken for a while after use. If any abnormalities are observed, this drug should be discontinued immediately, treated areas should be protected from sunlight and appropriate measures should be taken.

Over-the-counter drugs
Preparations Containing Ketoprofen (dermatologic preparation)

[When not to use the product]	This drug should not be used in the following persons: Persons who have experienced an allergic reaction (e.g., rash/redness, itching, contact dermatitis) after using the following drug products: Antipyretic analgesics containing tiaprofenic acid, topical anti-inflammatory analgesics containing suprofen, hypolipidaemic drug containing fenofibrate. Persons who have experienced an allergic reaction (e.g., rash/redness, itching, contact dermatitis) after using the following products: Products containing oxybenzone or octocrylene (e.g., sunscreen, perfume) Persons who have experienced photosensitivity. The following products should not be used concomitantly with this drug: Products containing octocrylene (e.g., sunscreen)

<References> (including provisionally translated titles)

1) Pharmaceuticals and Medical Devices Safety Information No.173 (January 2002)
2) Veyrac G, Paulin M, Milpied B, et al. Results of a French nationwide survey of cutaneous side effects of ketoprofen gel reported between September 1996 and August 2000. Therapie. 2002;57:55-64
3) Pharmaceuticals and Medical Devices Safety Information No.186 (February 2003)
4) http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/07/WC500094975.pdf
5) Material 7, The 6th Meeting of 2010 Subcommittee on Drug Safety Committee on Drug Safety Pharmaceutical Affairs and Food Sanitation Council (Safety measures against adverse reactions to topical ketoprofen and its risk classification)
   http://www.mhlw.go.jp/stf/shingi/2r9852000000tv0u.html (only available in Japanese language)

2

Research on System for Receiving Adverse Reaction Information from Patients

1. Introduction: adverse reactions reporting by patients

Adverse drug reaction reporting plays a very important role in drug safety measures. Under the Japanese adverse reaction reporting system, over 30,000 cases of adverse reaction have been reported every year by pharmaceutical companies and healthcare providers, such as physicians.

In Europe and the US, more countries have recently introduced systems for adverse reactions reports by patients. In 1993, the US Food and Drug Administration (FDA) started to receive adverse reaction reports from patients. The UK officially started a system to receive adverse reaction reports from patients in 2008 based on a pilot study conducted by the Medicines and Healthcare Products Regulatory Agency (MHRA) in 2003. Direct patient reporting is now considered important since adverse reaction reports by patients may be a useful indicator of safety issues.

Taking recent trends into consideration, the Japanese adverse reaction reporting system, which focuses on only adverse reaction reports from healthcare providers, is about to be changed to also receive reports from patients.

The final proposal by the Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Recurrence of Yakugai (Drug-induced Suffering) (April 28, 2010) advocated "the need for a scheme to effectively use adverse reaction information reported by patients (a scheme to effectively use adverse reaction information provided by patients)."

The "Research on System for Receiving Adverse Reaction Information from Patients" (hereinafter referred to as "the Research;" chief researcher, Professor Mayumi Mochizuki, Faculty of Pharmacy, Keio University) was started in FY 2009 supported by Health and Labour Sciences Research Grants. As part of the Research, a pilot study to receive adverse reaction reports from patients via the Internet started in January 2011 based on the results of the preceeding research.

The outline of the Research and the pilot study is introduced in the following sections.

The MHLW and the PMDA are currently having discussions to develop the system for adverse reactions reporting by patients as early as possible based on future results of the Research.

2. Outline of the Research

(1) Objective

The objective of the Research is to investigate problems and their solutions in the process of developing and introducing a system for adverse reactions reporting by patients in Japan.

(2) Past activities

The following activities were performed in FY 2009:

(i) A survey on the perception of consumers, physicians, and pharmacists towards adverse reactions and development of a draft of the Adverse Reaction Reporting Form
(ii) A survey on the current systems for adverse reactions reporting by patients in the US and Europe
(iii) Developing question items in the reporting form to ensure collection of accurate adverse reaction information from patients
(iv) Development of an Internet system for collecting adverse reaction reports
(v) Review of the data processing/analysis methods

A draft of the Adverse Reaction Reporting Form developed with reference to the foreign reporting forms such as those in the US, the UK, the Netherlands and the Internet system for collecting adverse reaction reports developed as one of the ways to report in FY 2009 were further reviewed in FY 2010. In consequence, an Internet system for collecting adverse reaction reports from patients has been developed, using the developed Adverse Reaction Reporting Form.

3. Pilot study of the Research Group

Using the Internet system for collecting adverse reaction reports from patients, a pilot study is currently being conducted to evaluate the usability of the system and identify problems (started on January 10, 2011; to be completed on July 31, 2011). The system for collecting adverse reaction reports from patients is available on the Research Group website, and there is a link from the PMDA website.

Numerous reports during the pilot study will enable identification of various problems concerning the patient reporting system and proposals for a better patient reporting system. Therefore, patients are encouraged as much as possible to know about the pilot study. Your cooperation in publicizing the pilot study would be appreciated.

<References>

1) "The Research on System for Receiving Adverse Reaction Information from Patients," Research report of the Health and Labour Sciences Research Grants in FY2009 (Pharmaceutical and Medical Device Regulatory Science Research Project)
(Executive summary of the research report) http://mhlw-grants.niph.go.jp/ (only available in Japanese language)

2) "Review on the Pharmaceutical Administration to Prevent Recurrence of Yakugai (Drug-induced suffering) (final proposal)", Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Recurrence of YakugaiSimilar Sufferings, April 28, 2010.
http://www.mhlw.go.jp/shingi/2010/04/dl/s0428-8a.pdf (only available in Japanese language)

The cooperation of general consumers in the pilot study for drug reaction reporting is greatly appreciated.
URL: http://rx.di-research.jp/ (only available in Japanese language)

3

Revision of Precautions (No. 222)

(1) Drugs

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 30, 2010.

1 <Psychotropics>

Atomoxetine Hydrochloride

[Brand Name] Strattera Capsules 5 mg, 10 mg, 25 mg (Eli Lilly Japan K.K.)

[Contraindications]

Patients with past or present phaeochromocytoma.

2 <Ophthalmic Agents>

Carteolol Hydrochloride (ophthalmic solution)

[Brand Name] MIKELAN OPHTHALMIC SOLUTION 1% (Otsuka Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Bradyarrhythmia including atrioventricular block, sick sinus syndrome, and sinus arrest, congestive cardiac failure, or coronary spastic angina: bradyarrhythmia including atrioventricular block, sick sinus syndrome, and sinus arrest, congestive cardiac failure, or coronary spastic angina may occur. If such symptoms are observed, administration should be discontinued, and appropriate measures should be taken.

3 <Cardiovascular agents-Miscellaneous>

Lanthanum Carbonate Hydrate

[Brand Name] Fosrenol Chewable Tablets 250 mg, 500 mg (Bayer Yakuhin, Ltd.)

[Precautions of Dosage and Administration] Patients should be instructed to completely chew up this drug and swallow it with saliva or a small amount of water, because this drug does not dissolve properly when swallowed without chewing, Some patients who swallowed this drug without chewing have had intestinal perforation or ileus. Patients who have difficulty in chewing (e.g., elderly patients) should take this drug after crushing the tablet.

[Careful Administration]

Patients with intestinal diverticulum [intestinal perforation has been reported.]
Patients with a history of peritonitis or abdominal surgery [ileus has been reported.]
Patients with past or present gastrointestinal ulcer [exacerbation or relapse of symptoms has been reported.]

[Adverse Reactions (clinically significant adverse reactions)]	**Intestinal perforation, ileus**: intestinal perforation or ileus may occur. Patients should be carefully monitored. If any abnormalities including persistent abdominal pain or vomiting suggestive of these disorders are observed, administration of this drug should be discontinued, abdominal examination, CT, X-ray, or ultrasound should be performed, and appropriate measures should be taken. In some cases, it has been reported that this drug was found unchewed in the patient's intestine by an imaging test. **Haemorrhage of digestive tract, gastrointestinal ulcer**: haematemesis, melaena, and gastric, duodenal or colonic ulcer may occur. Patients should be carefully monitored. If any abnormalities are observed, abdominal examination, endoscopy, X-ray, or CT should be performed, and appropriate measures such as discontinuing administration should be taken.
[Precautions concerning Use]	This drug should be swallowed after being chewed up completely. [Aspiration of this drug associated with incomplete chewing has been reported. Some patients who swallowed this drug without chewing have had intestinal perforation or ileus.]

4 **<Thyroid and parathyroid hormone preparations>**

Thiamazole

[Brand Name]	MERCAZOLE Tablet 5 mg, MERCAZOLE Injection 10 mg (Chugai Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Polyarthritis**: polyarthritis or migratory arthritis may occur. If such symptoms are observed, appropriate measures including discontinuing administration should be taken.

5 **<Blood and body fluid agents-Miscellaneous>**

Cilostazol

[Brand Name]	Pletaal tablets 50 mg (Otsuka Pharmaceutical Co., Ltd)
[Adverse Reactions (clinically significant adverse reactions)]	**Gastric and duodenal ulcer**: haemorrhagic gastric and duodenal ulcer may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

6 **<Antidotes>**

Sugammadex Sodium

[Brand Name]	BRIDION Intravenous 200 mg, 500 mg (MSD K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms**: shock and anaphylactoid symptoms (e.g., flushing, urticaria, erythematous rash, wheezing, decreased blood pressure, tachycardia, swollen tongue, pharyngeal oedema) may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be immediately taken.

7 **<Antidotes>**

Deferoxamine Mesilate

[Brand Name]	Desferal for injection 500 mg (Novartis Pharma K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Acute renal failure, renal tubular disorder**: acute renal failure and renal tubular disorder may occur. Patients should be carefully monitored. If such symptoms are observed, administration should be discontinued, and appropriate measures should be taken.

8 <Antimetabolites>

Capecitabine

[Brand Name]	XELODA Tablet 300 (Chugai Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Serious enterocolitis**: haemorrhagic enterocolitis, ischaemic enterocolitis, or necrotising enterocolitis may occur. Patients should be carefully monitored, and if symptoms including severe abdominal pain, diarrhoea, or bloody stool are observed, administration should be discontinued, and appropriate measures should be taken. **Serious neuropsychiaric disorders (e.g., leukoencephalopathy)**: Symptoms including gait disturbance, paralysis, extrapyramidal symptoms, ataxia, coordination disturbance, balance disorder, dyslalia, disturbed consciousness, lethargy, confusion, amnesia, impaired orientation, perceptual disturbance, or urinary incontinence may occur. These symptoms may occur as early symptoms of leukoencephalopathy. Patients should be carefully monitored, and if such symptoms are observed, administration should be discontinued.

9 <Antineoplastics-Miscellaneous>

Gefitinib

[Brand Name]	Iressa Tablets 250 (AstraZeneca K.K.)
[Important Precautions]	When using this drug, the latest information such as "Lung Cancer Clinical Practice Guideline" of the Japan Lung Cancer Society should be referred to.

10 <Antivirals>

Etravirine

[Brand Name]	INTELENCE Tablets 100 mg (Janssen Pharmaceutical K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Rhabdomyolysis**: Rhabdomyolysis characterized by myalgia, feeling of weakness, increased CK (CPK) , increased blood myoglobin, and increased urine myoglobin may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. Caution should be exercised for development of acute renal failure due to rhabdomyolysis.

11 <Vaccines>

Yellow Fever Vaccine

[Brand Name]	Yellow Fever Vaccine (Sanofi Pasteur)
[Adverse Reactions (clinically significant adverse reactions)]	**Nervous system disorders including cerebrospinal meningitis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, convulsion, and bulbar palsy**: nervous system disorders including cerebrospinal meningitis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, convulsion, and bulbar palsy may occur. Patients should be carefully monitored after vaccination. If any abnormalities are observed, appropriate measures should be taken.

(2) Medical Devices

This section presents details of revisions to the Precautions section of package inserts and brand names of medical devices that have been revised in accordance with the Notifications dated December 3, 2010.

1 Inferior Vena Cava Filter

[1] Permanent inferior vena cava filter

[Brand Name] Greenfield Vena Cava Filter (Boston Scientific Japan K.K.), VENA CAVA FILTER SYSTEM FOR JUGULAR OR FEMORAL APPROACH (B.Braun Aesculap Japan co., Ltd.), Simon Nitinol Filter (Medicon, Inc.), Gunther Tulip Vena Cava Filter (Femoral/Jugular), Gianturco-Roehm Bird's Nest Vena Cava Filter Set (Cook Japan), Cordis TRAPEASE, Cordis OPTEASE (Johnson & Johnson K.K.), ALN VENA CAVA FILTER (Piolax Medical Devices, Inc.)

[Warnings]

WARNINGS

Adverse events including filter fracture, filter migration, and filter embolization associated with long-term use have been reported. The filter condition should be monitored by periodical follow-up after placement. If filter fractures or other adverse events are observed, additional treatment should be considered as appropriate.

[2] Optional retrievable vena cava filters (filters which can be retrieved with a dedicated device within a certain period following placement or can be left in the patient as a permanent device)

[Brand Name] Gunther Tulip Vena Cava Filter (Femoral/Jugular) (Cook Japan), Cordis OPTEASE (Johnson & Johnson K.K.), ALN VENA CAVA FILTER (Piolax Medical Devices, Inc.)

[Warnings]

WARNINGS

Removal of this product is recommended, if continuous use of this product is not medically necessary and it can be removed safely, after considering the patient's risk.

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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 collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions.

EPPV is specified as a condition of approval.

(As of January 1, 2011)

Nonproprietary name Brand name on	Name of the marketing authorization holder	Date of EPPV initiate
Metformin Hydrochloride/Pioglitazone Hydrochloride METACT Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	July 6, 2010
Ramelteon ROZEREM Tablets 8 mg	Takeda Pharmaceutical Company Limited	July 6, 2010
Lenalidomide Hydrate Revlimid Capsules 5 mg	Celgene K.K.	July 20, 2010*1 August 20, 2010*2
Olopatadine Hydrochloride ALLELOCK Tablets 2.5, 5*3	Kyowa Hakko Kirin Co., Ltd.	July 23, 2010
Pazufloxacin Mesilate PASIL INTRAVENOUS DRIP INFUSION 300 mg, 500 mg*4	Toyama Chemical Co., Ltd.	July 23, 2010
Pazufloxacin Mesilate Pazucross INJECTION 300, 500*4	Mitsubishi Tanabe Pharma Corporation	July 23, 2010
Budesonide Pulmicort 100 μg Turbuhaler 112 doses, Pulmicort 200 μg Turbuhaler 56, 112 doses*5	AstraZeneca K.K.	July 23, 2010
Lansoprazole Takepron capsules 15, Takepron OD Tablets 15	Takeda Pharmaceutical Company Limited	July 23, 2010*6 August 20, 2010*7
Darbepoetin Alfa (Genetical Recombination) NESP INJECTION 10 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 15 μg/1 mL PLASTIC SYRINGE, NESP 20 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 30 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 40 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 60 μg/0.6 mL PLASTIC SYRINGE, NESP 120 μg/0.6 mL PLASTIC SYRINGE, NESP INJECTION 180 μg/0.9 mL PLASTIC SYRINGE	Kyowa Hakko Kirin Co., Ltd.	August 26, 2010
Ambrisentan Volibris Tablets 2.5 mg	GlaxoSmithKline K.K.	September 17, 2010
Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg	Nippon Shinyaku Co., Ltd.	September 17, 2010

Levetiracetam E Keppra Tablets 250 mg, 500 mg	UCB Japan Co., Ltd.	September 17, 2010
Abatacept (Genetical Recombination) ORENCIA FOR I.V. INFUSION 250 mg	Bristol-Myers K.K.	September 21, 2010
Temsirolimus TORISEL Injection 25 mg	Pfizer Japan Inc.	September 22, 2010
Paclitaxel Abraxane I.V. Infusion 100 mg	Taiho Pharmaceutical Co., Ltd.	September 24, 2010
Teriparatide (Genetical Recombination) FORTEO s.c. injection kit 600 μg	Eli Lilly Japan K.K.	October 1, 2010
Telmisartan/Amlodipine Besilate Micamlo Combination Tablets AP	Nippon Boehringer Ingelheim Co., Ltd.	October 7, 2010
Pazufloxacin Mesilate PASIL INTRAVENOUS DRIP INFUSION 1000 mg	Toyama Chemical Co., Ltd.	October 13, 2010
Pazufloxacin Mesilate Pazucross INJECTION 1000 mg	Mitsubishi Tanabe Pharma Corporation	October 13, 2010
Bazedoxifene Acetate Viviant Tablets 20 mg	Pfizer Japan Inc.	October 13, 2010
Laninamivir Octanoate Hydrate INAVIR DRY POWDER INHALER 20 mg	Daiichi Sankyo Company, Limited	October 19, 2010
Botulinum Toxin Type A BOTOX for injection 50 Unit, 100 Unit*8	GlaxoSmithKline K.K.	October 27, 2010
Adalimumab (Genetical Recombination) HUMIRA Subcutaneous Injection 40 mg Syringe 0.8 mL*9	Abbott Japan Co., Ltd.	October 27, 2010
Olanzapine Zyprexa Tablet 2.5 mg, 5 mg, 10 mg, Zyprexa Fine Granule 1 %, Zyprexa Zydis Tablet 5 mg, 10 mg*10	Eli Lilly Japan K.K.	October 27, 2010
Pregabalin LYRICA Capsules 25 mg, 75 mg, 150 mg*11	Pfizer Japan Inc.	October 27, 2010
Peramivir Hydrate RAPIACTA Bag for Intravenous Drip Infusion 300 mg, RAPIACTA Vial for Intravenous Drip Infusion 150 mg*5	Shionogi & Co., Ltd.	October 27, 2010
Polyethylene Glycol Treated Human Normal Immunoglobulin Venoglobulin IH 5% I.V. 0.5 g/10 mL, 1 g/20 mL, 2.5 g/50 mL, 5 g/100 mL*12	Benesis Corporation	October 27, 2010
Drospirenone/Ethinylestradiol YAZ Combination Tablet	Bayer Yakuhin, Ltd.	November 16, 2010
Olopatadine Hydrochloride ALLELOCK OD Tablets 2.5, 5	Kyowa Hakko Kirin Co., Ltd.	November 25, 2010
Eltrombopag Olamine REVOLADE Tablets 12.5 mg, 25 mg	GlaxoSmithKline K.K.	December 10, 2010
Nepafenac Nevanac Ophthalmic Suspension 0.1%	Alcon Japan Ltd.	December 10, 2010
Bendamustine Hydrochloride TREAKISYM Injection 100 mg	SymBio Pharmaceuticals Limited	December 10, 2010
Levocetirizine Hydrochloride		December 10, 2010

Xyzal Tablets 5 mg	GlaxoSmithKline K.K.	
Diquafosol Sodium DIQUAS ophthalmic solution 3%	Santen Pharmaceutical Co., Ltd.	December 13, 2010
Tolvaptan Samsca tablets 15 mg	Otsuka Pharmaceutical Co., Ltd.	December 14, 2010
Sodium Hyaluronate Crosslinked Polymer/Sodium Hyaluronate Crosslinked Polymer Crosslinked with Vinylsulfone SYNVISC 2 mL (intra-articular injection)	Genzyme Japan K.K.	December 14, 2010
Exenatide Byetta Subcutaneous Injection 5 μg Pen 300, 10 μg Pen 300	Eli Lilly Japan K.K.	December 17, 2010
Triamcinolone Acetonide MaQaid intravitreal injection 40 mg	Wakamoto Co., Ltd.	December 24, 2010

*1 The originally approved indication for “treatment of patients with relapsed or refractory multiple myeloma”

*2 An additional indication for “treatment of patients with myelodysplastic syndrome associated with a chromosome 5q deletion”

*3 An additional administration for “pediatrics (aged 7 and older)”

*4 An additional indication for “treatment of patients with sepsis, applicable microorganism; *Streptococcus pneumonia*”

*5 An additional administration for “pediatrics”

*6 An additional indication for “treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of low-dose aspirin”

*7 An additional indication for “treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of non-steroidal anti-inflammatory drugs”

*8 An additional indication for "treatment of patients with upper limb spasms or lower limb spasms"

*9 An additional indication for "remission induction or maintenance therapy for moderate or severe active Crohn's disease (limited to patients who are not adequately responsive to conventional therapy)"

*10 An additional indication for "treatment of manic symptoms in patients with bipolar disorder"

*11 An additional indication for "treatment of patients with peripheral neuropathic pain"

*12 An additional indication for “improvement of muscular weakness associated with polymyositis or dermatomyositis (limited to patients who are not adequately responsive to steroids)”