Pharmaceuticals and Medical Devices Safety Information

No. 298 January 2013

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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, 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

ADH	Antidiuretic hormone
ADRs	Adverse drug reactions
Alb	Albumin
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
ALP	Alkaline phosphatase
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
ATL	Adult T-cell leukemia
CC-A	Composite Component A
CCR	Chemokine receptor
CK (CPK)	Creatine kinase (Creatine phosphokinase)
Cr	Creatinine
CRP	C-reactive protein
DIC	Disseminated intravascular coagulation
DIHS	Drug-induced hypersensitivity syndrome
EPPV	Early Post-marketing Phase Vigilance
ETP+PSL	Etoposide, prednisolone
Hb	Hemoglobin
HBe	Hepatitis B envelope
HBs	Hepatitis B surface
HBV-DNA	Hepatitis B virus-Deoxyribonucleic acid
HCV-RNA	Hepatitis C virus-Ribonucleic acid
IC	Integrated circuit
IgM-HBc	Immunoglobulin M-Hepatitis B core
IPF	Idiopathic pulmonary fibrosis
IT	Information technology
ITF	Interleaved Two of Five
IU	International unit
JAN	Japanese Accepted Names for Pharmaceuticals
JIS	Japanese Industrial Standards
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
mPSL	Methylprednisolone
PT	Prothrombin Time
PTP	Press through package
Q&A	Questions and Answers
RBC	Red blood cell count
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
TEN	Toxic epidermal necrolysis
THP-COP	Pirarubicin, vincristine, cyclophosphamide, prednisolone
UA	Uric acid
VP-16	Etoposide
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

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Partial Amendment of the "Guidance for Bar Code Labeling on Prescription Drugs" for the Prevention of Medical Accidents

1. Introduction

The Guidance for Bar Code Labeling on Prescription Drugs was amended for prevention of medical accidents by the "Partial Amendment of the 'Guidance for Bar Code Labeling on Prescription Drugs'" (Joint HPB/EAD Notification No. 0629-1 and PFSB/SD Notification No. 0629-1, by the Director of the Economic Affairs Division [EAD], Health Policy Bureau [HPB] and by the Director of the Safety Division [SD], Pharmaceutical and Food Safety Bureau [PFSB], MHLW, dated June 29, 2012).

Bar code labeling has already been exercised for ampules and vials of specified biological products, biological products and injections (excluding biological products). With the present revision, bar codes will be also labeled on the press through package (PTP) sheets of oral medicines and the tubes of external medicines.

In addition, as a result of this amendment, Japanese Accepted Names for Pharmaceuticals (JAN) codes displayed on distribution packaging units such as a box containing 100 PTP sheets, and Interleaved Two of Five (ITF) codes labeled on a carton packaging box containing 10 distribution packaging units of boxes will be eliminated.

This section presents the background for developing bar code labeling on prescription drugs, an outline of the amendment, and implementation schedules. Healthcare professionals are encouraged to utilize bar codes for medical safety.

2. Background

The assurance of medical safety including the prevention of health injury due to mix-up of prescription drugs is an important challenge for healthcare policy. The causes for mix-up of prescription drugs include similarity in the name and appearance of prescription drugs. To address this matter, notifications listed in **Table 1** have been issued, and measures for the prevention of medical accidents due to similarity in the drug name and appearance have been taken.

Table 1 Major notifications about measures for the prevention of medical accidents due to similarity in the name and appearance of prescription drugs

Title of notification (including provisional translation)	Issued by
Handling of Labels and Brand Names of Drugs for the Prevention of Medical Accident	PMSB Notification No. 935 of Secretary-General of PMSB, MHLW, dated September 19, 2000
Thorough implementation of Measures for the Prevention of Medical Accident Due to the Similarity of Drug Brand Names and Appearances	PFSB Notification No. 1127003 of Secretary-General of PFSB, MHLW, dated November 27, 2003
Reinforcement and Thorough implementation of Measures for the Prevention of Drug-related Medical Accident	PFSB Notification No. 0602009 of Secretary-General of PFSB, MHLW, dated June 2, 2004
Points to be Considered for Giving Brand Names When Filing Approval Applications for Generic Prescription Drugs	PFSB/ELD Notification No. 0922001 of Director of the Evaluation and Licensing Division (ELD), PFSB, MHLW, dated September 22, 2005
Giving Brand Names of Prescription Combination Drugs and Heparin Products (Injections) and Handling of Labels of Solvents Attached to Injections	Joint PFSB/ELD Notification No. 0922001 and PFSB/SD Notification No. 0922001 of Director of the ELD, PFSB, and of Director of the SD, PFSB, MHLW, dated September 22, 2008
Reinforcement and Thorough implementation of Measures for the Prevention of Medical Accident Due to the Similarity of Drug Brand Names (Request for alert)	Joint HPB Notification No. 1204001 and PFSB Notification No. 1204001 of Secretary-General of the HPB, and of the Secretary-General of the PFSB, MHLW, dated December 4, 2008

In addition to these measures, in order to prevent medical accidents due to the mix-up of prescription drugs, necessity of a new measure was pointed out to mechanically distinguish prescription drugs without relying on humans. The "Promotion of Total Medical Safety Measures" prepared on April 2002 by the "Discussion Group on Medical Safety Measures" states that "the standardization of code labels for drugs should be considered by the government to further promote the use of bar code checks for the purpose of ensuring accurate and easy product distinction with the use of bar code checks." Then, in December 2003, as a measure for "products" such as drugs, the "Urgent Appeal for Measures of Medical Accident" of the Minister of Health, Labour and Welfare was issued to require "thorough safety control of drugs by, for example, using two-dimensional codes and IC tags, organization of a database for evaluation of similarity in drug names and appearance, and clarification of conditions for prescribing drugs especially requiring careful handling such as anticancer drugs."

In the revised Pharmaceutical Affairs Law (PAL) enforced in July 2003, an obligation for recording for specified biological products was legislated. When specified biological products are used in patients, medical institutions and pharmacies are required to record and retain the name of the patient, and information such as the name of the product and lot number or code, and if necessary, provide marketing authorization holders (MAHs) with such information. Also, when selling specified biological products and biological products to medical institutions and pharmacies, distributors such as drug wholesalers are required to provide the MAHs with the name of the purchaser and information such as the name of the product, lot number or code, quantity and expiration date. In addition, from the perspective of ensuring the traceability of prescription drugs, the standardization of IT systems and code formats for distribution has been required for products other than biological products.

In response to this trend, MHLW presented the "Guidance for Bar Code Labeling on Prescription drugs" in the "Practice of Bar Code Labeling on Prescription drugs" (PFSB/SD Notification No. 0915001 of the Director of the SD, PFSB, MHLW, dated September 15, 2006; partially revised by the PFSB/SD Notification No.0301001 of the Director of the SD, PFSB, MHLW, dated March 1, 2007) to enable mechanical check of products using bar codes for the purpose of not only preventing mix-up of prescription drugs but also ensuring the traceability of prescription drugs (see the "Pharmaceuticals and Medical Devices Safety Information No. 229" issued on October 16, 2006). Based on this, MAHs are required to perform bar code labeling on all packaging units including

dispensing packaging units for specified biological products, biological products and injections, and on distribution packaging units for oral and external medicines. For products released since September 2008, new bar codes in accordance with this notification have been labeled. New bar code labeling was not required for dispensing packaging units of oral or external medicines because technical development etc. for each packaging form was not completed at that time.

Thereafter, technical development of new bar code labeling for each packaging form of dispensing packaging units of oral and external medicines was undertaken by the relevant industries and companies so that new bar codes can be technically labeled on these packaging forms. In response to this, the draft of the amended Guidance was prepared, and public comments were collected from March 28 to June 10, 2011. Based on the collected comments and the previous discussions, the Guidance was amended by the "Partial Amendment of the 'Guidance for Bar Code Labeling on Prescription Drugs'" (Joint HPB/EAD Notification No. 0629-1 and PFSB/SD Notification No. 0629-1, by the Director of the EAD, HPB and by the Director of the SD, PFSB MHLW, dated June 29, 2012).

3. Outline of the amendment of the "Guidance for Bar Code Labeling on Prescription Drugs

This section mainly explains parts changed as a result of this amendment of the Guidance and parts particularly requiring attention of relevant parties such as medical institutions and pharmacies. For more information, see the end of this report as a reference.

(1) Objectives

By labeling a product-specific, machine-readable bar code for dispensing packaging units (e.g., PTP sheet and single-dose packed powder) of prescription drugs,

- to identify products mechanically for the prevention of medical accidents due to mix-ups.
- to trace drugs from MAHs and distributors to patients and ensure traceability.

(2) Products subject to labeling and labeling data

Products subject to new bar code labeling are prescription drugs. MAHs should make required labeling (◎) and optional labeling (○) in accordance with the types and packaging units of drugs as listed in **Table 2** (see Note 1 of **Table 2**). Based on this amendment of the Guidance, thick-framed items in **Table 2** are newly subject to required labeling. New bar code labeling is required to be performed for dispensing packaging units of oral and external medicines.

There will be no change for the method of numbering commodity codes and JAN codes.

Table 2 Prescription drugs subject to bar code labeling

Types of prescription drugs	Dispensing packaging unit			Distribution packaging unit			Supply packaging unit			
	comm-odity code	Expira-tion date	Lot number or code	comm-odity code	Expira-tion date	Lot number or code	comm-odity code	Expira-tion date	Quantity	Lot number or code
Specified biological products	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎
Biological products	◎	○	○	◎	◎	◎	◎	◎	◎	◎
Injections	◎	○	○	◎	○	○	○	○	○	○
Oral medicines	◎*	○	○	◎	○	○	○	○	○	○
External medicines	◎*	○	○	◎	○	○	○	○	○	○

Note 1) Dispensing packaging unit, distribution packaging unit and supply packaging unit refer to the following:

Dispensing packaging unit

A dispensing packaging unit is the minimum packaging unit in which MAHs pack drugs for marketing.

Example: A PTP sheet or bottle for tablets and capsules, or a single-dose package for powder, a bottle or tube of external medicines, and an ampule or vial for injections.

Distribution packaging unit

A distribution packaging unit is usually the minimum packaging unit in which distributors such as wholesalers sell products to purchasers such as medical institutions and pharmacies.

Example: A box of 100 dispensing packaging units, i.e., PTP sheets, for tablets and capsules, a box of 1000 single-dose packages for powder, a box of 100 tubes for external medicines, or a box of 10 ampules for injections

Supply packaging unit

A supply packaging unit is usually a packaging unit comprising multiple distribution packaging units packed by MAHs.

Example: A carton containing 10 distribution packaging units of boxes

Note 2) Based on the former Guidance, specified biological products, biological products and injections marked "◎" are specified to be required labeling for new bar codes. For commodity codes ("*") of dispensing packaging unit for oral and external medicines, the former Guidance stipulate that the implementation schedules will be notified separately since technologies, such as bar code labeling for each packaging style, are under development and aimed to be completed in 3 to 5 years by relevant industries and companies.

Note 3) As for optional labeling for distribution packaging units and supply packaging units, expansion of coverage will be discussed based on the future status of labeling and their use.

(3) Implementation schedules of new bar code labeling

1) New bar code labeling has been made for all kinds of packaging units for specified biological products, biological products or injections or distribution packaging units for oral medicines or external medicines.
2) For dispensing packaging units of oral medicines and external medicines other than biological products, labeling is to be newly required pursuant to this revision. New bar codes will be labeled on products released by MAHs after July 2015 (July 2016 for products with special reasons such as those manufactured only once a year).
3) Information (expiration date, quantity and lot number or code) specified in **Table 2** to be optional labeling for distribution packaging units and supply packaging units (hereinafter referred to as "distribution packaging units, etc.") is to be sequentially labeled from MAHs which can perform new bar code labeling.

(4) Elimination of JAN codes on distribution packaging units and ITF codes on supply packaging units

Currently, JAN bar codes of Japanese Industrial Standards (JIS) X0501 (Bar Code Symbol for Uniform Commodity Code) are displayed on distribution packaging units, and ITF bar codes of JIS

X0502 (Bar Code Symbol for Dispatch Unit Code) are displayed on supply packaging units.

JAN codes and ITF codes will be labeled on prescription drugs released by MAHs until September 2013 but then will be sequentially deleted. With this amendment of the Guidance, these bar codes shall not be labeled on prescription drugs released by MAHs after July 2015 (July 2016 for products with special reasons such as those manufactured only once a year).

4. Request for healthcare professionals

As described above, the "Guidance for Bar Code Labeling on Prescription Drugs" has been amended to essentially require labeling of new product bar codes on dispensing packaging units of oral and external medicines after a period for interim measures. In addition, from the viewpoint of traceability and efficacy of distribution, optional labeling (expiration date and lot number/code) on distribution packaging units and supply packaging units is to be required to be sequentially implemented by companies which can perform bar code labeling. In the future, in accordance with the amended Guidance, new bar codes will be labeled on all prescription drugs including dispensing packaging units, and items such as devices and packaging materials responding to this are anticipated to be developed and become available.

Healthcare professionals are requested to collaborate on the utilization of new bar codes to be labeled for not only preventing mix-up accidents of prescription drugs but also ensuring traceability such as lot, expiration date, and inventory management, as well as promoting the efficiency of distribution of prescription drugs.

In addition, JAN codes on distribution packaging units and ITF codes on supply packaging units will be eliminated; thus, if these codes are used for distribution and inventory management, please consider changing the control method.

[Related URL]

- Partial Amendment of the "Guidance for Bar Code Labeling on Prescription Drugs" (Joint HPB/EAD Notification No. 0629-1 and PFSB/SD Notification No. 0629-1, by the Director of the EAD, HPB and by the Director of the SD, PFSB MHLW, dated June 29, 2012) (only available in Japanese language)
- Questions and Answers (Q&A) on the Partial Amendment of the "Guidance for Bar Code Labeling on Prescription Drugs" (Administrative notice from the SD, PFSB, MHLW, dated June 29, 2012) (PMDA Website) (only available in Japanese language)
  http://www.info.pmda.go.jp/iryoujiko/iryoujiko_index.html
- The Public Comments on the "Partial Amendment of the 'Guidance for Bar Code Labeling on Prescription Drugs' (draft)" (only available in Japanese language)
  http://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495100347&Mo de=2
- Pharmaceuticals and Medical Devices Safety Information No. 229 "Guidance for Bar Code Labeling on Prescription Drugs for the Prevention of Medical Accident"
  (PMDA Website)
  http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-229.pdf

[References]

Numbering of commodity codes

A commodity code is a 14-digit code starting with "0" for dispensing packaging units, "1" for distribution packaging units, and "2" for supply packaging units, which is displayed at the front of the JAN code (hereinafter referred to as the "uniform commodity code") for each packaging unit.

An independent uniform commodity code should be assigned to each type of packaging unit for each prescription drug. In other words, separate uniform commodity codes should be given to products with a PTP sheet containing a different number of tablets or a box containing a different number of PTP sheets. Also, independent uniform commodity codes should be, in principle, assigned by each company marketing prescription drugs. For ethical narcotics and gases, independent numbers must be

given by each marketing authorization holder marketing them. Uniform commodity codes used in the past may not be reused for at least 10 years since marketing of the prescription drug with the same uniform commodity code was discontinued. However, uniform commodity codes used for specified biological products may never be reused after their marketing discontinuation.

Bar code symbol system, display order of data elements, and application identifiers

1. Dispensing packaging unit and distribution packaging unit

Any one of the GS 1 databar stacked, GS 1 databar limited, GS 1 databar stacked composite symbol with Composite Component A (CC-A), or GS 1 databar limited composite symbol with CC-A specified by the JIS X 0509 should be used.

When labeling only a commodity code, GS 1 databar limited should be used (however, if the labeling space is small, GS 1 databar stacked may be employed).

In addition to a commodity code, when an expiration date and lot number or code are displayed, the information should be labeled in the order of (1) commodity code, (2) expiration date, and (3) lot number or code using the GS 1 databar limited composite symbol with CC-A (however, if the labeling space is small, GS 1 databar stacked composite symbol with CC-A may be employed.). It is not permitted to omit labeling information such as only labeling Item (1) and (3).

2. Supply packaging unit

The information should be labeled in the order of (1) commodity code, (2) expiration date, (3) quantity, and (4) lot number or code using the Code 128 specified by the JIS X 0504. It is not permitted to omit labeling information such as only labeling Item (1) and (3).

2

Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated December 4, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Temozolomide

Brand Name (name of company)	TEMODAL Capsules 20 mg, 100 mg, TEMODAL Infusion 100 mg (MSD K.K.)
Therapeutic Category	Alkylating agents
Indications	Malignant glioma

PRECAUTIONS (underlined parts are revised)

Important Precautions

Hepatitis due to reactivation of hepatitis B virus may occur in hepatitis B virus carriers or HBs antigen-negative patients after administration of this drug. Prior to treatment, the patient should be checked for hepatitis virus infection and appropriate measures should be taken before administration of this drug. After the start of administration of this drug, attention to the occurrence of signs or symptoms related to reactivation of hepatitis B virus should be paid by continuously monitoring results of liver function tests or hepatitis viral markers.

Adverse Reactions (clinically significant adverse reactions)

Pneumocystis pneumonia, infection: Serious infections including opportunistic infection such as pneumocystis pneumonia or sepsis may occur. In addition, fulminant hepatitis or hepatitis due to reactivation of hepatitis B virus may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken. Particularly, the long-term use of this drug may increase the risk of occurrence of infections with or without steroids. Careful attention should be paid to long term-use. Disseminated intravascular coagulation (DIC), acute renal failure, and respiratory failure, etc. have been reported as complications of sepsis.

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 and 7 months (April 1, 2009 to November 12, 2012)

- Cases associated with reactivation of hepatitis B virus: 4 cases (1 fatal case)

The number of patients using this drug per year estimated by MAHs: Approximately 3,500 (2011)

Launched in Japan: September 2006 (oral dosage form)
May 2010 (injectable dosage form)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Mixed oligo-astrocytoma (viral hepatitis carrier)	100 mg for 42 days	**Fulminant hepatitis (B), decreased lymphocytes, gastrointestinal haemorrhage** The patient did not receive prophylactic administration of nucleoside analog before the onset of the adverse reactions. A steroid was used before the onset of the adverse reactions

				(prednisolone, from 36 days before administration to the start of administration of temozolomide). Transfusion was not performed before the onset of the adverse reactions. The patient had been a hepatitis B virus carrier from before administration of temozolomide, but it is unknown whether there was an opportunity for infection with hepatitis B virus before the onset of the adverse reactions. 34 days before administration: The patient was positive for hepatitis B surface (HBs) antigen. 15 days before administration: Left temporal lobe tumourectomy was performed. Day 1 of administration: Temozolomide + radiotherapy were started. Administration of interferon beta was started. Performance status of the patient at the start of administration of temozolomide was 1. Day 28 of administration: Lymphocytes decreased and administration of interferon beta was discontinued. Administration of temozolomide was continued. Day 43 of administration (day of completion): Temozolomide + radiotherapy (total dose, 54 Gy) were completed. 1 day after completion: The patient was discharged from the hospital. 44 days after completion (day of onset): General malaise and jaundice were noted (fulminant hepatitis [B] occurred). Discontinuation of administration of temozolomide was determined. Plasma exchange was performed. Administration of nucleoside analog (entecavir) was started. 47 days after completion: The patient was positive for HBs antigen and hepatitis B envelope (HBe) antibody. The patient was negative for HBs antibody, immunoglobulin M-hepatitis B core (IgM-HBc) antibody, and HBe antigen. 48 days after completion: Administration of nucleoside analog (entecavir) was discontinued. 49 days after completion: The patient died of fulminant hepatitis (B). Hepatic encephalopathy occurred (stage V: deep coma [no reaction to pain stimulation]). Haemorrhage symptom was noted (gastrointestinal haemorrhage).
	Concomitant medications: interferon beta			

Laboratory Examination

	34 days before administration	Day 5 of administration	44 days after completion (day of onset)	47 days after completion	49 days after completion
HBs antigen	Positive	-	-	Positive (> 2000.0)	-
HBs antibody	-	-	-	Negative (1.2)	-
IgM HBc antibody	-	-	-	Negative (0.3)	-
HBe antigen	-	-	-	Negative (0.1)	-

HBe antibody	-	-	-	Positive (100.0)	-
HBV-DNA level (LogIU/mL)	-	-	-	4.7	-
AST (GOT) (IU/L)	43	34	4530	462	355
ALT (GPT) (IU/L)	28	32	3310	373	274
LDH (IU/L)	233	243	611	809	-
ALP (IU/L)	482	275	801	363	-
γ-GTP (IU/L)	89	51	57	22	-
Total bilirubin (mg/dL)	0.4	0.4	8.3	6.7	7.6
Direct bilirubin (mg/dL)	0.1	-	3.7	-	1.7
Albumin (g/dL)	4.6	3.7	3.8	2.9	-
PT (%)	102.3	123.5	Unmeasurable	5.8	Unmeasurable
WBC (/mm^3)	10040	3430	6120	8550	9350
Lymphocytes (%)	24.4	28.9	11.8	2.0	-
Neutrophils (%)	70.1	63.8	80.5	96	-

2 Telaprevir

Brand Name (name of company)	TELAVIC Tablets 250 mg (Mitsubishi Tanabe Pharma Corporation)
Therapeutic Category	Antivirals
Indications	Improvement of the following viraemia in patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C: (1) Patients with high blood HCV RNA level who are treatment-naïve (2) Patients who are non-responders or relapsers to interferon monotherapy or combination therapy with ribavirin

PRECAUTIONS (underlined parts are revised)

Warnings

WARNINGS

Serious skin disorders associated with general symptoms such as toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), drug-induced hypersensitivity syndrome (DIHS), etc. may occur in concomitant use of peginterferon alfa-2b (genetical recombination) and ribavirin. Caution should be exercised for the following matters. This drug should be used in collaboration with a dermatologist.

Important Precautions

Serious skin disorders associated with general symptoms such as toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), drug-induced hypersensitivity syndrome (DIHS), etc. may occur in concomitant use of peginterferon alfa-2b (genetical recombination) and ribavirin. Caution should be exercised for the following matters. If any serious skin disorders are observed or if any of the symptoms caused by serious skin disorders are suspected (blister, epidermolysis, mucosal erosion/ulcer, eye disease, the occurrence of marked general symptoms related to rash, etc.), administration of this drug, peginterferon alpha 2b (genetical recombination) and ribavirin should be discontinued immediately and appropriate measures such as having the patient visit a dermatologist should be taken.

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome, or erythema multiforme may occur. Patients should be carefully monitored, and if pyrexia, blister, epidermolysis, mucosal erosion/ulcer, eye disease, etc. 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) for the past 1 year (from initial marketing to October 19, 2012)

- Toxic epidermal necrolysis: 2 cases (1 fatal case)

The number of patients using this drug per year estimated by MAHs: Approximately 6,900 (from initial marketing to September 2012)

Launched in Japan: November 2011

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Improvement of viraemia in patients with chronic hepatitis C (insomnia) (hypertension) (hyperuricaemia) (allergic rhinitis)	1500 mg for 56 days, 1000 mg for 7 days	**Toxic epidermal necrolysis, pyrexia, malaise, increased blood uric acid, renal impairment, erythema, diarrhoea, decreased appetite, multi-organ failure** The patient previously underwent treatment with interferon + ribavirin. During dual therapy, the patient developed skin eruption (10% or less of the body surface area), oedema of the face and lower legs, and hepatic dysfunction; and therefore he received treatment with glycyrrhizin/glycine/L-cysteine and steroids. Also at the time of administration of interferon, renal function was slightly aggravated, and therefore oral administration of allopurinol tablets (100 - 300 mg/day, until 8 days after discontinuation) was started at an early stage. Day 1 of administration: The patient started receiving telaprevir 1500 mg/day, ribavirin 800 mg/day, peginterferon α-2b 1.4 μg/kg/week (triple combination therapy). Pyrexia and malaise occurred. When the dual therapy was performed, skin eruption, oedema, etc. were observed as adverse reaction symptoms, and therefore telaprevir was started at a reduced dose of 1500 mg/day. Day 3 of administration: Mefenamic acid (750 mg/day) and rebamipide tablets (300 mg/day, until 8 days after discontinuation of telaprevir) were orally administered. Day 5 of administration: Uric acid level increased and renal impairment occurred. Day 6 of administration: From the start of administration, cutaneous pruritus and red flare of upper and lower limbs were observed. Grade 1: 50% or less of the body surface area (localised), with pruritus. Diarrhoea occurred. Bifidobacterium granular powder (3 g/day, until 8 days after discontinuation of telaprevir) were orally administered. Day 7 of administration: Oral administration of prednisolone was started (20 mg, until Day 14). Day 12 of administration: The patient was discharged from the hospital. Day 15 of administration: Etizolam tablets (1 mg/day, until 8 days after discontinuation) and loperamide hydrochloride capsules (2 mg/day, until 8 days after discontinuation) were orally administered. Pyrexia and malaise remitted. As the symptoms had improved, the dose of prednisolone was

				reduced to 10 mg (10 mg/day, until Day 23 of administration). Day 22 of administration: Inappetence occurred. Hydrocortisone for injection (100 mg/day, until Day 24 of administration) was intravenously administered. Day 24 of administration: Betamethasone/gentamicin lotion (2 mL/day) and diphenhydramine cream (3 g/day) were applied to the skin. The dose of prednisolone was increased to 20 mg (20 mg/day, until Day 28 of administration). Day 29 of administration: Diarrhoea and inappetence remitted. The dose of prednisolone was reduced to 15 mg (15 mg/day, until Day 56 of administration). Due to a high uric acid, the dose of allopurinol tablets (300 mg/day) was increased. Day 36 of administration: Red flare remitted. Day 43 of administration: Increased uric acid level and renal impairment remitted. Day 50 of administration: Skin eruption occurred on the face. The patient was followed up with an external medicine. Day 57 of administration: Skin eruption occurred on the face and thighs. An ulceration was seen around the injection site of interferon on the left upper arm. The dose of telaprevir was reduced to 1000 mg/day. The dose of prednisolone, which had been reduced, was re-increased to 20 mg (20 mg/day, until 9 days after discontinuation of telaprevir). Transdermal Ketoprofen, a percutaneous anti-inflammatory analgesic, (1 patch/day, until 9 days after discontinuation of telaprevir) was applied. Betamethasone/gentamicin ointment (1.2 g/day, until 9 days after discontinuation of telaprevir) was applied. Day 64 of administration (day of onset) (day of discontinuation): The skin symptoms worsened, and rash with ulcer on both upper limbs and skin eruption of the face developed (proportion of rash to body surface area: 40%). Administration of telaprevir was discontinued. Brotizolam orally-disintegrating tablets (0.25 mg/day, until 8 days after administration of telaprevir) were orally administered. Glycyrrhizinate injection (80 mL/day, until 9 days after discontinuation of telaprevir) was intravenously administered. 3 days after discontinuation: At the time of the re-visit, rash appeared on the extremities and the patient also had skin ulcer. Therefore the patient was admitted to the hospital and methylprednisolone pulse therapy was started. Methylprednisolone for injection (1000 mg/day, until 6 days after discontinuation of telaprevir) was intravenously administered. 4 days after discontinuation: Glucose-added acetate maintenance solution injection (200 mL/day, until 9 days after discontinuation of telaprevir), vitamin (B1, B6, B12) preparations for intravenous injection (1 V/day, until 9 days after discontinuation of telaprevir), and heparin 10 units (10 mL/day until 9 days after discontinuation of telaprevir) were intravenously administered. 6 days after discontinuation:

				Diclofenac sodium (25 mg/day as needed, until 7 days after discontinuation of telaprevir) was administered. 7 days after discontinuation: Oral food intake was possible and the general status was stable. Ulcer was noted on both upper limbs, but was slightly improving. At the time of the rounds, the ulcer site had become dry and the skin had risen, thereby confirming improvement. Loxoprofen tablets (180 mg/day, until 8 days after discontinuation of telaprevir) were orally administered. Methylprednisolone for injection (500 mg/day, until 8 days after discontinuation of telaprevir) was intravenously administered. Until this day, the patient was able to take the food orally and talked with nurses normally. 8 days after discontinuation: The disease state rapidly worsened, ulcer and skin eruption of both upper limbs were exacerbated, and epidermal necrosis with blister spread on both lower limbs. The symptoms started to occur on different regions. Administration of ribavirin was discontinued. Diclofenac sodium (25 mg/day as needed, until 9 days after discontinuation of telaprevir) was administered. 9 days after discontinuation: Oral food intake, which had been possible until the time of evening meal the previous day, became difficult. When the patient scratched or touched the skin, the skin tore open and became haemorrhagic. The epidermis of the extremities and body trunk exfoliated like a thermal burn and formed blisters. Epidermolysis occurred just by pressing. As epidermal necrosis started rapidly on the whole body, the patient was transferred to Hospital A where there is a collaborating dermatology department in accordance with emergency procedure. Grade 3, blister, epidermolysis accounting for 40% of the body surface area, no mucosal symptoms, no eye symptoms. General symptom: multi-organ failure. Administration of peginterferon α-2b was discontinued. High-calorie transfusion (1003 mL/day), electrolyte transfusion (500 mL/day), carbazochrome sodium sulfonate injection 0.5% 10 mL (10 mL/day), tranexamic acid injection (250 mg/day), cefazolin sodium for injection 1 g (1 g/day), saline injection (100 mL/day), human normal immunoglobulin G for intravenous injection (2500 mg/day), methylprednisolone for injection (1000 mg/day) were intravenously administered. 10 days after discontinuation: The patient died from suspected toxic epidermal necrolysis at the hospital to which he was transferred.
	Concomitant medications: peginterferon α-2b (suspected drug), ribavirin (suspected drug), ursodesoxycholic acid, liverhydrolysate-containing preparation, monoammonium glycyrrhizinate/glycine/L-cysteine, zolpidem tartrate, clotiazepam, losartan potassium, hydrochlorothiazide, olopatadine			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Improvement of viraemia in patients with chronic hepatitis C	1500 mg for 39 days	**Toxic epidermal necrolysis, bacterialpharyngitis, cytomegalovirus test positive, increased blood beta-D-glucan, hyperuricaemia, anaemia, constipation, haemorrhoids** The patient previously had treatment with interferon + ribavirin. Day 1 of administration: The patient started receiving telaprevir 1500 mg/day, ribavirin 400 mg/day, and peginterferon α-2b 1.4 μg/kg/week (triple combination therapy). Day 4 of administration (day of onset): Redness and pruritus occurred on the abdomen. Betamethasone ointment (0.05%) (*quantum libet*/day as needed, application to the skin) and heparinoid ointment (*quantum libet*/day as needed, application to the skin) were prescribed. Hyperuricaemia occurred. Uric acid (UA) increased to 7.2. Oral administration of allopurinol (200 mg/day, until 31 days after discontinuation) was started. Day 6 of administration: Red papule associated with pruritus was found from the side chest to lower back on the body trunk and on fingers. The patient was diagnosed with Grade 2 for these symptoms by a dermatologist. Clobetasol ointment (0.05%) (*quantum libet*/day as needed, application to the skin) was prescribed. Day 8 of administration: It was confirmed by the dermatologist that skin eruption did not spread. Day 15 of administration: Anaemia developed. Skin eruption tended to resolve. Administration of antiallergic agents was continued. Administration of ribavirin (200 mg/day) was changed. Day 29 of administration: Body temperature of 37.4°C, swollen cervical lymph nodes were observed. Day 30 of administration: Erythema appeared except the areas around the eyes on the face. Pyrexia of 37.5°C developed. Fexofenadine tablets and clobetasol ointment were administered. Day 31 of administration: Tulobuterol tape (2 mg/day, until 44 days after discontinuation, application to the skin), prednisolone ointment (quantum libet/day, until 42 days after discontinuation, application to the skin), luliconazole solution (quantum libet/day, application to the skin) were administered. Day 33 of administration: Pyrexia of 38.0°C or higher developed. Grain-sized or rice-sized skin eruption was seen all over the body. Administration of fexofenadine was discontinued and fexofenadine was switched to levocetirizine tablets (5 mg/day, per oral). Day 34 of administration: Eosinophils increased to 10.6% (WBC 3770/mm^3). Facial rash tended to improve. Administration of prednisolone (20 mg/day, per oral) was started. Day 36 of administration:

				The dose of prednisolone was decreased to 10 mg. Administration of peginterferon α-2b was discontinued. Day 38 of administration: Erythema appeared again. The dose of prednisolone was increased to 20 mg. Prednisolone ointment and clobetasol scalp lotion (quantum libet/day, application to the skin) were administered concurrently. Day 39 of administration: Exudativum erythema appeared. The dose of levocetirizine was increased (10 mg/day). Day 40 of administration (day of discontinuation): The symptom was aggravated and evaluated to be Grade 3. The patient had been treated in hospital. Diffuse erythema with marginal infiltration developed. Purpura occurred on the upper palate in the oral cavity. Both administration of ribavirin and telaprevir were discontinued. The patient was admitted to the dermatology department. The dose of prednisolone was increased to 60 mg. WBC was 8200/mm^3 (eosinophils 7.3%) 1 day after discontinuation: Olopatadine tablets (10 mg/day, per oral) were administered. 2 days after discontinuation: Prednisolone (50 mg/day, until 11 days after discontinuation, per oral) was administered. 12 days after discontinuation: The dose of prednisolone was decreased to 40 mg. Pharynx pain occurred, and swollen lymph nodes were observed. 19 days after discontinuation: Pyrexia of 38.0°C or higher developed. Drip infusion of ceftriaxone preparation (2 g/day, until 26 days after discontinuation, intravenous injection) was started for bacterial pharyngitis (haemophilus influenzae-positive). 20 days after discontinuation: Prednisolone (60 mg/day, until 22 days after discontinuation, per oral) was administered. Erosion appeared on the lips and in the oral cavity. Fluorometholone ophthalmic solution 0.1% (quantum libet/day as needed, until 49 days after discontinuation, ocular administration) and ofloxacin ophthalmic ointment 0.3% (quantum libet/day as needed, until 36 days after discontinuation, application to the eye) were administered. 21 days after discontinuation: Skin biopsy was performed. Epidermal necrosis was noted. Zinc oxide ointment (10%) simple ointment (quantum libet/day as needed, until 27 days after discontinuation, application to the skin) was administered. 23 days after discontinuation: Steroid pulse therapy (methylprednisolone 1000 mg/day for 3 days, until 25 days after discontinuation, intravenous injection) was administered. Acetaminophen (300 mg/day as needed, until 31 days after discontinuation, per oral) was administered. 24 days after discontinuation: Genital erosion was confirmed. 25 days after discontinuation: Oral erosion was improved. 26 days after discontinuation: Prednisolone (60 mg/day, until 28 days after discontinuation) was orally taken. Administration of ceftriaxone preparation was

				discontinued. 29 days after discontinuation: Red-purple skin eruption spread, and oral and genital erosions also worsened. Plasma exchange and steroid pulse therapy were started. Methylprednisolone (1000 mg/day, until 31 days after discontinuation, intravenous injection), lidocaine injection 1% (10 mL/day, until 31 days after discontinuation, topical injection at the time of operation), hydrocortisone for injection (100 mg/day, until 31 days after discontinuation, in dialysis circuit), calcium gluconate injection 8.5% (10 mL/day, until 31 days after discontinuation, in dialysis circuit) were administered. Cytomegalovirus antigenemia 17 + 11. 30 days after discontinuation: Ganciclovir (500 mg/day, until 48 days after discontinuation, intravenous injection) was administered. 32 days after discontinuation: Administration of water-soluble prednisolone for injection (90 mg/day, until 39 days after discontinuation, drip infusion) was started. One tablet of sulfamethoxazole/trimethoprim preparation was administered. Fentanyl for injection 10 μg/mL/day, ketamine for intravenous injection 0.75 mg/mL/day, lidocaine for drip infusion 7 mg/mL/day were intravenously administered. 33 days after discontinuation: Xylocaine jelly 2% (quantum libet/day as needed, until 38 days after discontinuation, application to the skin), hydrophilic ointment (quantum libet/day as needed, until 38 days after discontinuation, application to the skin), betamethasone/gentamicin ointment (quantum libet/day as needed, until 38 days after discontinuation, application to the skin) were administered. 34 days after discontinuation: Skin eruption worsened (erythema red increased on the body trunk and extremities). 35 days after discontinuation: Human normal immunoglobulin G (10 g/day, until 39 days after discontinuation, intravenous injection) was administered. 40 days after discontinuation: The dose of prednisolone was decreased to 80 mg. Blood test showed cytomegalovirus antigenemia 11 + 8 and β-D glucan 28.6 pg/mL, showing high levels. Administration of water-soluble prednisolone for injection (80 mg/day, until 44 days after discontinuation, drip infusion) was administered. 44 days after discontinuation: Administration of sulfamethoxazole/trimethoprim preparation tablets (12 tablets in 3 divided doses/day, until 46 days after discontinuation, per oral) were started. β-D glucan level was normal and cytomegalovirus was negative. 45 days after discontinuation: The dose of prednisolone was reduced to 65 mg. Heparinoid lotion (quantum libet/day as needed, until 51 days after discontinuation, application to the skin) and water-soluble prednisolone for injection (65 mg/day, until 47 days after discontinuation, drip infusion) were administered.

				47 days after discontinuation: The dose of sulfamethoxazole/trimethoprim preparation tablets was reduced (1 tablet/day, per oral). 48 days after discontinuation: Prednisolone (50 mg/day, until 50 days after discontinuation) was orally taken. Administration of ganciclovir was discontinued. 51 days after discontinuation: The dose of prednisolone was reduced (40 mg/day, until 56 days after discontinuation, per oral). 57 days after discontinuation: The dose of prednisolone was reduced (30 mg/day, per oral). Skin eruption became pigmented, with no erosion. Oral erosion was improved. Genital ulcer was improved. 67 days after discontinuation: TEN remitted.
	Concomitant medications: ribavirin (suspected drug), peginterferon α-2b (suspected drug), allopurinol (suspected drug), prednisolone (suspected drug)			

3 Pramipexole Hydrochloride Hydrate

Brand Name (name of company)	(1) BI-Sifrol Tablets 0.125 mg, 0.5 mg (Nippon Boehringer Ingelheim Co., Ltd.) (2) Mirapex-LA Tablets 0.375 mg, 1.5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic Category	Antiparkinsonian agents
Indications	(1) 1. Parkinson's disease 2. Moderate to severe idiopathic restless legs syndrome (2) Parkinson's disease

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Syndrome inappropriate ADH (SIADH): Syndrome inappropriate ADH (SIADH) accompanied by hyponatraemia, blood hyposmosis, increased urine sodium, hypersthenuria, convulsions, or disturbed consciousness may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures such as restricting fluid intake should be taken.

Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

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 and 6 months:

[April 1, 2009 to September 28, 2012]

- Cases associated with syndrome inappropriate ADH (SIADH): 1 case (no fatal cases)

[April 4, 2009 to October 1, 2012]

- Rhabdomyolysis-associated cases: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAHs:

(1) Approximately 83,000 (October 2011 - September 2012)

(2) Approximately 10,000 (from initial marketing to September 2012)

Launched in Japan: (1) January 2004

(2) July 2011

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Parkinson's disease (none)	0.25 mg/day for 18 days ↓ 0.5 mg/day for 126 days ↓ 1.5 mg/day for 595 days ↓ 2.25 mg/day For 651 days ↓ 3 mg/day for 90 days ↓ 1.5 mg/day for 4 days ↓ 0.5 mg/day for 2 days ↓ 1.5 mg/day for 46 days	**Pleural effusion, peripheral oedema, scrotal oedema, inappropriate antidiuretic hormone secretion, spinal compression fracture** Weight: 40 kg Day 1 of administration: The patient started receiving pramipexole hydrochloride hydrate. Approximately 4 years after administration: Lumbar compression fracture occurred. Day 1391 of administration: The dose of pramipexole hydrochloride hydrate was increased to 3 mg/day. Day 1480 of administration: Oedema developed from the thighs to scrotum. The patient was admitted to the hospital for pleural effusion and dyspnoea. Day 1481 of administration: The dose of pramipexole hydrochloride hydrate was reduced to 1.5 mg/day. Pleural effusion covering about one-fourth of the entire lungs was noted in the right and left lower lobes. Day 1485 of administration: The dose of pramipexole hydrochloride hydrate was reduced to 0.5 mg/day. Day 1486 of administration (day of discontinuation): Administration of pramipexole hydrochloride hydrate was discontinued. 9 days after discontinuation: Pleural effusion decreased. 12 days after discontinuation (Day 1 of readministration): As activities of daily life deteriorated, administration of pramipexole hydrochloride hydrate was resumed (1.5 mg/day). Day 19 of readministration: Scrotal oedema remitted. Pleural effusion/oedema and femoral oedema remitted once. Day 37 of readministration: Pleural effusion, femoral oedema, and hyponatremia (Na: 112 mEq/L) which was considered to be SIADH developed again. Day 46 of readministration (day of discontinuation of readministration): Administration of pramipexole hydrochloride hydrate was discontinued. 1 day after discontinuation of readministration: The patient was re-admitted to the hospital. Pleural effusion was noted in the entire right lower lobe and about one-fourth of the left lower lobe. 16 day after discontinuation of readministration: Pleural effusion and oedema were improved by restriction on water intake (Na: 135 mEq/L). 17 days after discontinuation of readministration: SIADH, pleural effusion, and femoral oedema remitted. 33 days after discontinuation of readministration: The patient recovered from lumbar compression fracture, but

				with sequela (numbness of lower limb).
	Concomitant medications: levodopa/benserazide hydrochloride, lansoprazole, droxidopa, amantadine hydrochloride			

Laboratory Examination

	Day 908 of administration	Day 1468 of administration	Day 1480 of administration	Day 1482 of administration	5 days after discontinuation	Day 44 of readministration	1 day after discontinuation of readministration	16 day after discontinuation of readministration
ADH (pg/mL)	-	-	-	-	-	-	3.4	-
Na (mEq/L)	136	127	125	121	135	112	112	135
Cl (mEq/L)	-	-	93	-	-	76	-	98
Alb (g/dL)	-	-	3.3	-	-	2.7	-	3.1
Hb (g/dL)	-	-	12.6	-	-	11.8	-	11.3
Cre (mg/dL)	-	-	0.46	-	-	0.44	-	0.4
Serum osmolality (mOsm/L)	-	-	258	-	-	-	232	276
Urine Na (mEq/L)	-	-	63	-	-	-	114	134

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Multiple system atrophy (hypertension)	0.125 - 0.375 mg/day for 63 days ↓ 0.75 mg/day for 61 days ↓ 1.5 mg/day for 58 days ↓ 2 mg/day for 308 days ↓ 4 mg/day for 27 days	**Rhabdomyolysis** Weight: 65 kg Day 1 of administration: The patient started receiving pramipexole hydrochloride hydrate for multiple system atrophy. Day 491 of administration: The dose of pramipexole hydrochloride hydrate was increased to 4 mg/day. Day 517 of administration (day of discontinuation): While taking a bath, the patient felt sleepy in the bathtub and was unable to move his limbs. He called out loud but the neighborhood residents did not notice (Administration of pramipexole hydrochloride hydrate was discontinued). 1 day after discontinuation: The next morning, the patient pulled out the plug of the bathtub and drained the water by himself. A person living upstairs who noticed his shouts requested an ambulance. The patient was transported to the hospital. Hyper-creatinine kinase (CK)-emia and myoglobinaemia were found, and myalgia, muscle swelling, adynamia, and muscle rigidity were noted. The patient was admitted to the hospital for rhabdomyolysis (CK [CPK]: 11242 IU/L). Disturbed consciousness, marked sweaty, salivation, tachycardia, etc. were not noted. Fluid replacement was performed with 4500 mL/day of maintenance solution/extracellular fluid. 2 days after discontinuation: Fluid replacement was performed with 2500 mL/day of maintenance solution/extracellular fluid. 3 days after discontinuation: The patient started taking meals. The patient gradually recovered from hyper-CK-emia and

				myoglobinaemia. 9 days after discontinuation: The patient was discharged from the hospital (CK [CPK]: 282 IU/L). 16 days after discontinuation: The patient recovered from rhabdomyolysis.
	Concomitant medications: selegiline hydrochloride, zonisamide, levodopa/carbidopa hydrate, ropinirole hydrochloride, magnesium oxide, domperidone, aclatonium napadisilate			

Laboratory Examination

	Day 498 of administration	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	6 days after discontinuation	8 days after discontinuation	9 days after discontinuation
CK (CPK) (IU/L)	203	11242	6617	494	719	280	282
Serum myoglobin (ng/mL)	-	14073	599	385	95	108	-
AST (GOT) (IU/L)	19	200	157	120	43	28	-
ALT (GPT) (IU/L)	5	69	76	68	44	38	-
LDH (IU/L)	203	625	578	544	434	351	-
Cre (mg/dL)	0.8	0.86	0.79	0.81	0.73	0.78	-
CRP (mg/dL)	0.03	0.31	4.06	4.82	4.93	2.45	-
Body temperature (°C)	-	38.3	37.7	37.9	37.4	36.6	-

4 Mogamulizumab (Genetical Recombination)

Brand Name (name of company)	POTELIGEO Injection 20 mg (Kyowa Hakko Kirin Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma

PRECAUTIONS (underlined parts are revised)

Warnings

WARNINGS

Severe skin disorders associated with general symptoms such as toxic epidermal necrolysis (TEN) and oculomucocutaneous syndrome (Stevens-Johnson syndrome) have been reported. Treatment should be provided in collaboration with a dermatologist from the start of administration of this drug. In addition, attention should be paid to the following matters:

1) It has been reported that severe skin disorders may occur not only during administration of this drug but also for several weeks after completion of administration. Patients should be carefully monitored.
2) Appropriate measures (e.g. uses of corticosteroids, antiallergic agents, antihistamines) should be taken from the early stage after the onset of skin disorders. If severe skin disorders are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Adverse Reactions (clinically significant adverse reactions)

Severe skin disorders: Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), rash, etc. may occur during or after the administration of this drug. Appropriate measures (e.g. uses of corticosteroids, antiallergic agents, antihistamines) should be taken from the early stage after the onset of skin disorders. If severe skin disorders 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) for the past 5 months (from initial marketing to October 31, 2012)

- Toxic epidermal necrolysis-associated cases: 4 cases (1 fatal case)

The number of patients using this drug per year estimated by MAHs: Approximately 380 (from initial marketing to October 2012)

Launched in Japan: May 2012

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Adult T-cell lymphoma/ leukemia (diabetes mellitus)	70 mg administered 8 times at weekly intervals	**Stevens-Johnson syndrome** **Toxic epidermal necrolysis (TEN)** Before start of administration: The patient experienced marked abnormal hepatic function due to hepatic infiltration of adult T-cell leukemia (ATL). Abnormal liver function test values tended to improve with the regimen of pirarubicin, vincristine, cyclophosphamide, and prednisolone (THP-COP) and etoposide (VP-16) but were not adequate (bilirubin level: 2 or higher). Day 1 of administration: Administration of mogamulizumab (genetical recombination) 70 mg/day was started. The liver function test values were gradually improved by administration of mogamulizumab (genetical recombination). 18 days after administration: Considering the antitumor effect, administration of dexamethasone was started at 4 mg, and the dose was reduced to 2 mg, 1 mg, and 0.5 mg. 28 days after administration: Fifth administration of mogamulizumab (genetical recombination) was performed. Skin eruption (G1) appeared on the left knee, but had improved 7 days after administration. 35 days after administration: Sixth administration of mogamulizumab (genetical recombination) was performed. Mild fungal infection-like skin eruption appeared on the buttock (itraconazole was administered). At and after the sixth administration, the liver function test values tended to mildly increase. 42 days after administration: The patient recovered from skin eruption on the buttock. 49 days after administration (day of completion): Eighth administration of mogamulizumab (genetical recombination) was performed. 16 days after completion: Skin disorders and itching occurred on the cheeks and precordia. Itching also occurred in the eyes. Fexofenadine hydrochloride (60 mg × 2 times/day) was added to dexamethasone 0.5 mg which was being continued. Eye drops of steroid were administered. 21 days after completion: Skin disorders rapidly progressed.

				Unlike the previous skin eruption, they did not remit (skin eruption with peeling occurred on the face and precordia). 23 days after completion: Body temperature was 35.8°C. Conjunctival hyperaemia and lip erosion were observed as mucosal symptoms. Erythema appeared on the precordia, abdomen, and around the mouth. Epidermal necrotic disorder was noted on 20% of the surface of the whole body. The skin exfoliated on the cheeks, precordia, and around the mouth. The condition progressed so much that the skin peeled when the patient hunched his back for medical examination. Pharynx pain also developed. Treatment was started with methylprednisolone sodium succinate 250 mg/day and d-chlorpheniramine maleate. 24 days after completion: The patient was transported to another hospital by ambulance. Body temperature was 36.5°C. Conjunctival hyperaemia and lip erosion were observed as mucosal symptoms, and also a lesion was noted on the precordia. Erythema was noted on the precordia, abdomen, and around the mouth. Epidermal necrotic disorder was noted on 30% of the surface of the whole body, and the site that had exfoliated the preceding day spread to the abdomen. After that, the skin symptoms progressed from the upper limbs to lower limbs, and then blisters occurred on the thighs. 29 days after completion: Epithelization was noted on the face, but blisters remained on the lower limbs. 30 days after completion: The patient died from sepsis due to pseudomonad aeruginosa and multi-organ failure due to disseminated intravascular coagulation (DIC). Blisters on the lower limbs persisted. Lesions were noted on 80% of the whole body. Disease as cause of death: Sepsis due to pseudomonad aeruginosa
	Concomitant medications: acetaminophen, chlorpheniramine maleate, hydrocortisone, sulfamethoxazole/trimethoprim, sennoside, itraconazole, omeprazole, magnesium oxide, loxoprofen sodium hydrate, allopurinol, insulin aspart (genetical recombination), insulin glargine (genetical recombination), brotizolam, dexamethasone			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Adult T-cell lymphoma/ leukemia (hypertension, hyperlipidaemia)	48 mg administered 4 times at weekly intervals	**Toxic epidermal necrolysis (TEN)** Before start of administration: The patient was admitted to the hospital for detailed examination of increased white blood cell with atypical cells. A physical examination showed no appreciable findings. Pirarubicin, vincristine, cyclophosphamide, and prednisolone (THP-COP) regimen was performed but was

				not effective. The disease was controlled with etoposide and prednisolone (ETP + PSL). Administration of ETP was discontinued 2 days before administration of mogamulizumab (genetical recombination). The dose of PSL was gradually reduced. Day 1 of administration: Administration of mogamulizumab (genetical recombination) 48 mg/day was started. The patient had chills, shivering, and pyrexia (39°C) that were considered to be infusion reactions. 6 days after administration: Second administration of mogamulizumab (genetical recombination) was performed. Pyrexia, etc. was not occurred. Atypical lymphocyte count was several percent, showing a marked effect. 13 days after administration: Third administration of mogamulizumab (genetical recombination) was performed. The patient had a feeling of skin dryness and several tiny papules on the forearms. Since a marked treatment effect was noted, administration was performed while applying a steroid ointment to the skin. 20 days after administration (day of completion): Fourth administration of mogamulizumab (genetical recombination) was performed. 4 days after completion: Swelling was noted on the palm and dorsum of the foot. 5 days after completion: Generalised redness and pruritus were observed. Administration of prednisolone 30 mg was started in addition to topical steroids. 7 days after completion: Infiltrative erythema was observed on the back, extremities, precordia, lower limbs, palm, and dorsum of the hand. No event was almost noted on the face. 8 days after completion: Blisters formed at some sites of erythema. Itching occurred around the eyelids. Redness appeared on the oral mucosa. Steroid pulse therapy (methylprednisolone [mPSL] 1 g for 3 days) was performed. 12 days after completion: Blisters formed at the sites of infiltrative erythema. Tense blisters were noted on the left neck and the dorsum of the foot. Blisters on the back and chest were torn due to friction. MELOLIN gauze was used to protect the skin. Date unknown: Second steroid pulse therapy (mPSL 0.5 g for 3 days) was performed. 38 days after completion: The skin lesion almost peeled at the site of blister formation on the palm/foot sole, precordia, abdomen, and back. Skin regeneration was noted. Scab parts remained on some sites of the lower leg and the dorsum of the foot, but the condition improved significantly. 48 days after completion:

				The skin had almost recovered. Date unknown: Rehabilitation was started. The patient was able to walk and arrangements were started toward hospital discharge. Approximately 3 months after completion: The patient died from rapidly progressing renal failure. Disease as cause of death: Renal failure
	Concomitant medications: none			

3

Revision of Precautions (No. 242)

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 December 4, 2012 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 Cardiotonics

Digoxin
Deslanoside
Methyldigoxin

Brand Name

DIGOSIN Tablets 0.125 mg, 0.25 mg, DIGOSIN Powder 0.1%, DIGOSIN Elixir 0.05 mg/mL, DIGOSIN Injection 0.25 mg (Chugai Pharmaceutical Co., Ltd.)
and the others
Digilanogen Injection 0.4 mg (I'rom Pharmaceutical Co., Ltd.)
LANIRAPID Tablets 0.05 mg, 0.1 mg (Chugai Pharmaceutical Co., Ltd.)
and the others

Adverse Reactions (clinically significant adverse reactions)

Nonocclusive mesenteric ischaemia: Nonocclusive mesenteric ischaemia may occur resulting in intestinal necrosis in some cases. Patients should be carefully monitored, and if any symptoms such as severe abdominal pain and bloody stool are observed, administration of this drug should be discontinued and appropriate measures should be taken.

2 Cardiovascular agents-Miscellaneous

Ambrisentan

Brand Name

Volibris Tablets 2.5 mg (GlaxoSmithKline K.K.)

Important Precautions

The overseas clinical trial conducted in patients with idiopathic pulmonary fibrosis (IPF) showed that the risk of aggravation of IPF may be increased in association with administration of this drug. When this drug is administered to patients with pulmonary arterial hypertension associated with fibrillization of the lungs, the use of this drug should be carefully considered based on the risks and benefits involved in administration of this drug by means of such as consultation with a pulmonologist specializing in treatment of pulmonary fibrosis.

3 Hemostatics

Gelatin (sponge 2 cm × 6 cm × 0.7 cm, 8 cm × 12.5 cm × 1 cm)

Brand Name

Gelfoam (Pfizer Japan Inc.)

Contraindications

Patients with a history of hypersensitivity to ingredients of this drug

dverse Reactions (clinically significant adverse reactions)	**Shock, anaphylaxis**: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if abnormalities such as generalised redness, dyspnoea, or decreased blood pressure are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

4 **Hemostatics**

Gelatin (sponge 5 cm × 2.5 cm, 10 cm × 7 cm)

Brand Name	Spongel (Astellas Pharma Inc.)
Contraindications	Patients with a history of hypersensitivity to ingredients of this drug
Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylaxis**: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if abnormalities such as generalised redness, dyspnoea, or decreased blood pressure are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

5 **Antineoplastics-Miscellaneous**

Pazopanib Hdrochloride

Brand Name	Votrient Tablets 200 mg (GlaxoSmithKline K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Thrombotic microangiopathy**: Thrombotic microangiopathy such as thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome may occur. Patients should be carefully monitored through periodic tests, and if anaemia with schizocyte, decreased platelets, renal impairment, etc. are observed, administration of this drug should be discontinued and appropriate measures should be taken. **Pancreatitis**: Pancreatitis may occur. Patients should be carefully monitored. If any symptoms suggesting pancreatitis are observed, administration of this drug should be discontinued and appropriate measures should be taken.

6 **Non-main therapeutic purpose agents-Miscellaneous**

Gelatin (film)

Brand Name	Gelfilm, Ophthalmic Gelfilm (Pfizer Japan Inc.)
Contraindications	Patients with a history of hypersensitivity to ingredients of this drug
Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylaxis**: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if abnormalities such as generalised redness, dyspnoea, or decreased blood pressure are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of new drugs. 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 drugs 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 January 1, 2013)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg*1	Ferring Pharmaceuticals Co., Ltd.	December 21, 2012
Irbesartan/Amlodipine Besilate AIMIX Combination Tablet LD, HD	Dainippon Sumitomo Pharma Co., Ltd.	December 19, 2012
Olanzapine Zyprexa Rapid Acting Intra-Muscular Injection 10 mg	Eli Lilly Japan K.K.	December 3, 2012
Anagliptin SUINY Tab. 100 mg	Sanwa Kagaku Kenkyusho Co., Ltd.	November 30, 2012
Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL	Bayer Yakuhin, Ltd.	November 27, 2012
Stiripentol DIACOMIT DRYSYRUP 250 mg, 500 mg, DIACOMIT CAPSULES 250 mg	Meiji Seika Pharma Co., Ltd	November 27, 2012
Glycopyrronium Bromide seebri inhalation capsules 50 μg	Novartis Pharma K.K.	November 22, 2012
Tigecycline Tygacil Injection 50 mg	Pfizer Japan Inc.	November 22, 2012
Lubiprostone Amitiza Capsules 24 μg	Sucampo Pharma Ltd.	November 22, 2012
Botulinum Toxin Type A BOTOX for injection 50 Unit, 100Unit*2	GlaxoSmithKline K.K.	November 21, 2012
Everolimus AFINITOR tablets 5 mg, 2.5 mg*3	Novartis Pharma K.K.	November 21, 2012
Triamcinolone Acetonide MaQaid intravitreal injection 40 mg*4	Wakamoto Co., Ltd.	November 21, 2012
Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine TETRABIK Subcutaneous Injection Syringe	The Research Foundation for Microbial Diseases of Osaka University	October 31, 2012
Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine Quattrovac Subcutaneous Injection Syringe	The Chemo-Sero-Therapeutic Research Institute	October 31, 2012

Degarelix Acetate Gonax 80 mg for Subcutaneous Injection, Gonax 120 mg for Subcutaneous Injection	Astellas Pharma. Inc.	October 23, 2012
Clopidogrel Sulfate PLAVIX 25 mg Tablets, 75 mg Tablets*5	Sanofi-aventis K.K.	September 28, 2012
Tazobactam Sodium/Piperacillin Sodium ZOSYN for Intravenous Injection 2.25, 4.5*6	Taiho Pharmaceutical Co., Ltd.	September 28, 2012
Pazopanib Hydrochloride Votrient Tablets 200 mg	GlaxoSmithKline K.K.	September 28, 2012
Iguratimod KOLBET Tablets 25 mg	Toyama Chemical Co., Ltd.	September 12, 2012
Iguratimod Careram Tablets 25 mg	Eisai Co., Ltd.	September 12, 2012
Teneligliptin Hydrobromide Hydrate TENELIA Tablets 20 mg	Mitsubishi Tanabe Pharma Corporation	September 10, 2012
Formoterol Fumarate Hydrate Oxis 9 μg Turbuhaler 28 doses, 60 doses*7	AstraZeneca K.K.	September 3, 2012
Inactivated Poliomyelitis Vaccine (Salk Vaccine) IMOVAX POLIO subcutaneous	Sanofi Pasteur K.K.	August 31, 2012
Axitinib Inlyta Tablets 1 mg, 5 mg	Pfizer Japan Inc.	August 30, 2012
Ropinirole Hydrochloride ReQuip CR Tablets 2 mg, 8 mg	GlaxoSmithKline K.K.	August 28, 2012
Atomoxetine Hydrochloride Strattera Capsule 5 mg, 10 mg, 25 mg, 40 mg*8	Eli Lilly Japan K.K.	August 24, 2012
Sulbactam Sodium/Ampicillin Sodium UNASYN-S for Intravenous Use 0.75 g, 1.5 g, UNASYN-S KIT for Intravenous Use 1.5 g, 3 g*9, 10	Pfizer Japan Inc.	August 10, 2012
Budesonide/Formoterol Fumarate Hydrate Symbicort Turbuhaler 30 doses, 60 doses*11	AstraZeneca K.K.	August 10, 2012
Perflubutane SONAZOID FOR INJECTION 16 μL*12	Daiichi Sankyo Company, Limited	August 10, 2012
Sunitinib SUTENT Capsule 12.5 mg*13	Pfizer Japan Inc.	August 10, 2012
Apomorphine Hydrochloride Hydrate Apokyn subcutaneous injection 30 mg	Kyowa Hakko Kirin Co., Ltd.	July 27, 2012
Rotavirus Vaccine, Live, Oral, Pentavalent RotaTeq Oral Solution	MSD K.K.	July 20, 2012
Gabapentin Enacarbil Regnite Tablets 300 mg	Astellas Pharma. Inc.	July 10, 2012

*1 An additional indication for “treatment of patients with central diabetes insipidus”

*2 An additional indication for “treatment of patients with severe primary axillary hyperhidrosis”

*3 An additional indication for “treatment of patients with renal angiomyolipoma associated with tuberous sclerosis, subependymal giant cell astrocytoma associated with tuberous sclerosis”

*4 An additional indication for “treatment of patients with diabetic macular oedema”

*5 An additional indication for “prevention of thrombus and embolus formation in patients with peripheral arterial disease”

*6 An additional indication for “treatment of patients with peritonitis, intra-abdominal abscess, cholecystitis, or cholangitis”

*7 An additional indication for “remission of various symptoms associated with airway obstructive disorder in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema)”

*8 An additional indication for “treatment of patients with attention deficit/hyperactivity disorder (AD/HD) in adulthood”

*9 An additional indication for “Streptococcus pneumonia, Moraxella (Branhamella) catarrhalis”

*10 An additional administration for “severe infections”

*11 An additional indication for “remission of various symptoms in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema) (for patients who require concomitant use of inhaled corticosteroids and long acting inhaled beta-2 agonist)”

*12 An additional indication for “contrast enhanced imaging for breast mass lesion in mammary ultrasonography”

*13 An additional indication for “treatment of patients with pancreatic neuroendocrine tumour”