Pharmaceuticals and Medical Devices Safety Information

No. 227 August 2006

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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. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, Japanese only).

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This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).

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, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

1

Important Safety Information

This section presents contents of revisions, reference materials, and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 226).

1 Gemcitabine Hydrochloride

Brand Name (name of company)	Gemzar Injection 200 mg and 1 g (Eli Lilly Japan K.K.)
Therapeutic Category	Antimetabolites
Indications	Non-small cell lung cancer, pancreatic carcinoma, carcinoma of the biliary tract

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Serious hepatic function disorder with an increase in AST (GOT), ALT (GPT), Al-P, etc, jaundice may occur.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to March 31, 2006) (events for which a causality to the drug could not be denied)
• Hepatic function disorder, jaundice: 6 cases (of which 3 had a fatal case)
The number of patients treated with Gemcitabine estimated by MAH (Marketing Authorisation Holder): approximately 57000 (FY2005)
Marketed in Japan in: August 1999

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 70s	Non-small cell lung cancer (hypertension, emphysema, depression)	1200 mg twice 1000 mg 6 times	**Hepatic function disorder** 178 days before administration: Three courses of monotherapy with docetaxel hydrate for squamous cell carcinoma of the left inferior lobe of lung ($T_2N_0M_0$) were implemented. On day 1 of administration: Administration of this drug at 1200 mg (2 administrations and 1 washout period × 1 course) was initiated. 31 days after administration: Administration of this drug at 1000 mg (2 administrations and 1 washout period × 3 courses) was initiated. 87 days after administration: Symptoms of upper respiratory inflammation were observed in regular examination. Gatifloxacin hydrate at 200 mg was prescribed.	Company report

				90 days after administration: 10 days after the last administration, the patient came to the hospital due to strong general malaise. Hepatic function abnormal with AST (GOT) of 1460 IU/L and ALT (GPT) of 1267 IU/L was confirmed. The patient was hospitalized. Administration of glycyrrhizin/glycine/cysteine was initiated. All oral medicines were discontinued. In chest X-ray, only left lung tumor and old tuberculosis were confirmed. Since CRP was mildly high, at 3.91 mg/dL, intravenous injection of fosfomycin sodium was initiated. 92 days after administration: AST (GOT) 252 IU/L, ALT (GPT) 758 IU/L. 111 days after administration**:** AST (GOT) 20 IU/L, ALT (GPT) 21 IU/L. The patient recovered from hepatic function disorder.	
	Concomitant medications: alfacalcidol, amlodipine besilate, tocopherol nicotinate, bromazepam, triazolam, gatifloxacin hydrate				

Clinical Laboratory Values

	2 days before administration	65 days after administration	90 days after administration	92 days after administration	97 days after administration	111 days after administration
AST (GOT) (IU/L)	19	25	1460	252	34	20
ALT (GPT) (IU/L)	8	19	1267	758	151	21
Al-P (IU/L)	232	231	337	246	192	251
Total bilirubin (mg/dL)	0.4	--	0.5	0.6	--	--

AST: Asparate Aminotransferase ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 50s	Large cell lung cancer (pharyngeal cancer, hypertension)	1300 mg twice	**Hepatic failure** The patient had no past history of hepatic disease. History of alcohol consumption (3 flasks of sake/day) was noted. Approx. 1 month before administration: During antibiotic treatment for suspected pneumonia, mild liver disorder was admitted. The liver disorder was improved by discontinuation of drugs. In a detailed check, the patient was diagnosed with large cell lung cancer (large: $T_3N_2M_1$, stage IV). 26 days before administration: 135 mg of cisplatin and 100 mg of docetaxel hydrate were administered. On day 1 of administration: 1300 mg of this drug and 30 mg of vinorelbine ditartrate were administered. 7 days after administration: Last administration of 1300 mg of this drug and 30 mg of vinorelbine ditartrate was conducted. 8 days after administration: Platelet transfusion was initiated due to development of platelets decreased. Liver disorder developed. AST (GOT) 141 IU/L, ALT (GPT) 138 IU/L, Al-P 436 IU/L.	Company report

				9 days after administration: Blood transfusion of concentrated human red blood cells and administration of G-CSF were conducted for anaemia, and white blood cell decreased, respectively. 11 days after administration: AST (GOT) 665 IU/L, ALT (GPT) 679 IU/L, Al-P 668 IU/L. Administration of glycyrrhizin/glycine/cysteine was initiated. 13 days after administration: Clarithromycin, which had been administered since approximately 1 month before administration of this drug was initiated, was discontinued. 16 days after administration: AST (GOT) 1290 IU/L, ALT (GPT) 1155 IU/L, Al-P 502 IU/L, total bilirubin 11.5 mg/dL. Oral administration of ursodeoxycholic acid, use of fresh frozen human plasma (total of 8 units) and corticosteroid pulse therapy (1 g/day of methylprednisolone sodium succinate) were initiated. Obstructive jaundice was not confirmed. Hepatitis B and C viral markers were negative. In a detailed check, biliary dilatation, hepatic mass, and cardiac failure were excluded. Liver biopsy was not performed due to poor condition. 19 days after administration: Corticosteroid pulse therapy was completed. 21 days after administration: Administration of ursodeoxycholic acid was discontinued, because oral administration became difficult. 25 days after administration: The patient died from sudden progression of hepatic failure in early morning. Autopsy: not performed Cause of death: lung cancer and hepatic failure	
	Concomitant medications: vinorelbine ditartrate (suspected drug), clarithromycin				

Clinical Laboratory Values

	1 day before administration	8 days after administration	11 days after administration	15 days after administration	16 days after administration	18 days after administration
AST (GOT) (IU/L)	13	141	665	1300	1290	1235
ALT (GPT) (IU/L)	18	138	679	1067	1155	1166
Al-P (IU/L)	593	436	668	455	502	575
Total bilirubin (mg/dL)	--	--	--	--	11.5	14.5

AST: Asparate Aminotransferase ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase

2 Adsorbed Tetanus Toxoid

Brand Name (name of company)	Adsorbed Tetanus Toxoid “KAKETSUKEN” (The Chemo-Sero-Therapeutic Research Institute) Adsorbed Tetanus Toxoid “BIKEN” (Research Institute for Microbial Diseases, Osaka University) Adsorbed Tetanus Toxoid “SEIKEN” (Denka Seiken Co., Ltd.) Adsorbed Tetanus Toxoid “Hokken” (The Kitasato Institute) Adsorbed Tetanus Toxoid Kit “Takeda” (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Toxins, toxoids
Indications	This drug is used for the prevention of tetanus.

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant side reactions)]

Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms (redness generalized, dyspnoea, angioedema, etc.) may occur. Patients should be carefully monitored after inoculation. If abnormalities are observed, appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to June 14, 2006) (events for which a causality to the drug could not be denied)
• Shock, anaphylactoid symptoms: 3 cases (no fatal case)
The number of patients treated with Adsorbed Tetanus Toxoid estimated by MAH: approximately 700000 (FY2005)
Marketed in Japan in: 1965

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 40s	Contused wound on right thigh, tetanus immunisation (hepatic cirrhosis)	0.5 mL once	**Anaphylactic reaction, tracheal oedema** 30 minutes after inoculation: Redness of face and itching were observed. 90 minutes after inoculation: Redness generalized and face oedema (tracheal oedema) were noted, O_{2SAT} was decreased to 93%, blood pressure was 128/74 mmHg. Drip infusion was conducted. 5 hours after inoculation: Redness was improved. Hospitalization was recommended to the patient, but he refused and went home. 1 day after inoculation: The patient complained of general malaise. He refused blood sampling. The patient was instructed to visit hospital again the next day and to undergo blood sampling, but did not visit hospital again afterwards.	Company report
	Concomitant medications: none				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 20s	Tetanus immunization (none)	0.5 mL once	**Anaphylactic reaction, loss of consciousness** 2 minutes after inoculation: Since loss of consciousness, eyeballs raise upward, and slight convulsion developed, the patient was moved to a bed and vascular access was established. Blood pressure 99/55 mmHg, pulse 61, SpO_2 99% (indoor air). Flushed face, and wheezing found in chest auscultation were observed. 3 minutes after inoculation: Though consciousness recovered, the patient demonstrated marked feelings of weakness of limbs. During conversation, depressed level of consciousness occurred several times. 4 minutes after inoculation: (after recovery of consciousness) SpO_2 was 95%, and administration of oxygen was initiated. 17 minutes after inoculation: Intravenous injection of 125 mg of methylprednisolone was conducted. Breathing difficulty was improved rapidly, chest wheezing also disappeared. 22 minutes after inoculation: Blood pressure was 82/57 mmHg. 29 minutes after inoculation: 0.5 mg of epinephrine subcutaneous injection was conducted. Approx. 2 hours after inoculation: The patient was hospitalized. Consciousness was already lucid at the time of hospitalization. There were some incidences where the patient spaced out a little in the night. Approx. 3 hours after inoculation: Blood pressure was 108/62 mmHg. For anaphylactic reaction, there was only fluid replacement (lactated Ringer's solution, maintenance fluid) and no additional treatment was given after hospitalization. 1 day after inoculation: Consciousness was nearly completely lucid. Blood pressure was 80 to 90/50 to 60 mmHg (normal for the patient). The patient was steady recovered. 2 days after inoculation: Blood pressure was 90/60 mmHg. Consciousness was lucid, no drip infusion or administration of drugs was conducted. 3 days after inoculation: Consciousness was lucid, and no drug therapy was conducted. The patient was discharged from hospital. 7 days after inoculation: The patient made an outpatient visit to the hospital. Blood pressure was 88/58 mmHg.	Company report
	Concomitant medications: none				

3 Sodium Picosulfate
(product with the indication for bowel preparation before colon examination)

Brand Name (name of company)	Aperil Dry Syrup (Nichi-Iko Pharmaceutical Co., Ltd.) Konsuben Solution (Tsuruhara Pharmaceutical Co., Ltd.) Shinluck Solution (Iwaki Seiyaku Co., Ltd.) Chaldol Solution (Taiyo Yakuhin Co., Ltd.) Falestack Solution (Towa Pharmaceutical Co., Ltd.) Flurale Dry Syrup, Flurale Solution (TAKATA SEIYAKU Co., Ltd.) Berberon Solution (Maruko Pharmaceutical Co., Ltd.) Youpis Solution (ISEI Co., Inc.) Laxoselin Solution (Choseido Pharmaceutical Co., Ltd.) Laxodate Liquid (Kobayashi Kako Co., Ltd.) Laxoberon Solution (Teijin Pharma Limited)
Therapeutic Category	Purgatives, clysters
Indications	1. Various constipation 2. Postoperative defecation assistance 3. Promotion of defecation after administration of a contrast medium (barium sulfate) 4. Elimination of contents in intestine before an operation 5. Elimination of contents in intestine during preparation for colon examination (X ray, endoscopy)

<<**PRECAUTIONS** (underlined parts are additions)>>

[Contraindications]	Patients with <u>suspected</u> acute <u>abdomen</u>. <u>Patients with a history of hypersensitivity to any components of this drug.</u> <u>Patients with obstruction or suspected obstruction in the intestine (when this drug is used as bowel preparation before colon examination)</u>
[Careful Administration]	<if this drug is used as preparation for colon examination> <u>Patients with intestinal stenosis or severe constipation</u> <u>Patients with intestinal diverticulum</u> <u>Elderly</u>
[Important Precautions]	If using this drug as bowel preparation before colon examination, <u>enhanced gastrointestinal peristalsis lead to</u> elevation of intestinal pressure, and ischemic colitis <u>may occur. In addition, since intestinal obstruction leading to intestinal perforation may occur in patients with stenosis in the intestine, caution should be exercised to the following points upon administration</u>. <u>1) Daily defecation condition of patients should be observed. This drug should be administrated after confirming that there is a normal amount of defecation before administration or on the day before administration.</u> <u>2) If abnormalities such as abdominal pain are observed after administration, appropriate measures such as conducting an abdominal examination and imaging tests (simple X-ray, ultrasound, CT, etc.) should be taken.</u> <u>If this drug is used as preparation for colon examination at patients' home, patients should be instructed to avoid taking the drug when he/she is alone since it may be difficult to handle adverse reactions if any such reactions occur.</u>
[Adverse Reactions (clinically significant adverse reactions)]	<u>**Intestinal obstruction, intestinal perforation:** If this drug is used as preparation for colon examination, intestinal obstruction leading to intestinal perforation may occur in patients with stenosis in the intestine. Patients should be carefully observed. If any abnormalities such as abdominal pain are observed, appropriate measures should be taken.</u>
<Reference Information>	The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to February 28, 2006) (events for which a causality to the drug could not be denied) • Intestinal obstruction, intestinal perforation: 6 cases (no fatal case)

The number of patients treated with Picosulfate for a year estimated by MAH:
Approximately 5 million, of which 700000 used this drug as preparation for colon examination (FY2005)
Marketed in Japan in: 1980 (additional indication for preparation for colon examination: March 1992)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 50s	Endoscopy large bowel (aplastic anaemia, osteoporosis)	75 mg 1 day	**Intestinal obstruction** 7 days before administration: The patient noted fresh melaena during defecation, was referred to this department and received a consultation. Upon confirming that there was defecation and no exacerbation of constipation, this drug was prescribed as preparation for lower gastrointestinal endoscopy. On day 1 of administration: As preparation for colon examination, the patient took this drug (75 mL/10 mL) at home. In the nighttime, the patient felt sick and vomiting occurred. 1 day after administration: Dyspnoea developed in the morning. The patient was sent to hospital by ambulance. The patient complained of abdominal distension, pain in right leg, low back pain. In the afternoon, the patient was diagnosed with intestinal obstruction based on an X-ray test. Gastric tube was placed, and transanal ileus tube were inserted under lower gastrointestinal endoscopy. In the evening, due to consciousness decreased and blood pressure decreased, artificial respiration control and administration of dopamine hydrochloride were initiated. 2 days after administration: In early morning, cardiopulmonary resuscitation was performed. Around noon, death was confirmed. Diagnosis from pathological autopsy: #1. Acute intestinal necrosis accompanying obstructive colitis: Ileum (partial) to colon to rectum (due to rectal cancer described in #2.) #2. Rectal cancer (5 × 3 × 3 cm, moderately differentiated adenocarcinoma): no metastasis #3. Generalized bleeding tendency #4. Arteriosclerosis	Company report
	Concomitant medications: cetraxate hydrochloride, metenolone acetate, furosemide, spironolactone, prednisolone, potassium chloride, loxoprofen sodium				

Note) With regard to case No. 1, a causality between this drug and intestinal obstruction cannot be denied, but this case was evaluated such that a causality between this drug and death cannot be confirmed.

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 50s	Endoscopy large bowel (large intestine carcinoma, intestinal obstruction)	75 mg 1 day	**Intestinal perforation** 11 days before administration: The patient was hospitalized for intestinal obstruction. Ileus tube was inserted, intake of food and fluid was prohibited and central venous nutrition was implemented to promote improvement of symptoms. Symptoms were improved once. On day 1 of administration: To determine the cause of intestinal obstruction, a lower gastrointestinal endoscopy was planned, and this drug (75 mg/10 mL) was administered as pretreatment. 1 day after administration: Nausea, vomiting, and abdominal pain developed in early morning. Marked inflammatory reaction and metabolic acidosis were confirmed. Images of ascites, free air, and intrahepatic portal gas were confirmed in abdominal CT. Emergency operation was performed in the evening. Dark red-brown ascites with smell of stools, intestinal necrosis of a broad range from around terminal ileum to sigmoid colon, and mass accompanying perforations in sigmoid colon were confirmed. Necrotic intestine was excised. Afterwards, the symptoms disappeared through intensive care including endotoxin adsorption therapy, abdominal drainage, and administration of antibiotics. 62 days after administration: The patient recovered and was discharged from the hospital.	Company report
	Concomitant medications: amino acid/sugar/electrolytes, manganese chloride/zinc sulfate, multivitamin product for high-calorie infusion liquid, soybean oil				

2

Revision of PRECAUTIONS (No. 178)

This section presents details of revisions to the PRECAUTIONS section of package inserts, brand names of drugs that have been revised according to the Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 226) (excluding those presented in "1. Important Safety Information" of this Bulletin), together with reference materials.

1 <Skeletal muscle relaxants> Pancuronium Bromide

[Brand Name] Mioblock Intravenous 4 mg (Nippon Organon K.K.)

[Important Precautions] As this drug causes respiratory depression, controlled respiration must be performed until spontaneous respiration is recovered (a gas anesthesia apparatus or artificial respiration should be used).
Caution should be exercised in patients with past history of anaphylactic reactions caused by succinylcholine (suxamethonium chloride), as this product may also cause anaphylactic reactions in such patients.
To prevent complications such as respiratory depression and aspiration caused by residual curarization, extubation should be conducted after confirming that the patient's muscle relaxation has fully recovered.

<Reference Information> Company report

2 <Skeletal muscle relaxants> Vecuronium Bromide

[Brand Name] Musculax Intravenous 4 mg and 10 mg (Nippon Organon K.K.) and others

[Important Precautions] As this drug causes respiratory depression, controlled respiration should be performed until spontaneous respiration is recovered (a gas anesthesia apparatus or artificial respiration should be used).
Caution should be exercised in patients with past history of anaphylactic reactions caused by succinylcholine (suxamethonium chloride), as this product may also cause anaphylactic reactions in such patients.
To prevent complications such as respiratory depression and aspiration caused by residual curarization, extubation should be conducted after confirming that the patient's muscle relaxation has fully recovered.

<Reference Information> Company report

<Antispasmodics>

3 Scopolamine Butylbromide (oral dosage form, suppository)

[Brand Name] Buscopan Tablets (Nippon Boehringer Ingelheim Co., Ltd.), Butiburon Supp. (Nisshin Pharmaceutical Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms (nausea/vomiting, chills, pallor of skin, blood pressure decreased, dyspnoea, bronchospasm, oedema, and angioedema, etc.) may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

<Antispasmodics>

4 Scopolamine Butylbromide (injectable dosage form)

[Brand Name] Buscopan Injection (Nippon Boehringer Ingelheim Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms (nausea/vomiting, chills, pallor of skin, blood pressure decreased, dyspnoea, bronchospasm, oedema, and angioedema, etc.) may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

<Antihypertensives>

5 Alacepril, imidapril Hydrochloride, Enalapril Maleate, Captopril, Quinapril Hydrochloride, Cilazapril, Temocapril Hydrochloride, Delapril Hydrochloride, Trandolapril, Benazepril Hydrochloride, Perindopril Erbumine, Lisinopril

[Brand Name] Cetapril Tablets 12.5 mg, 25 mg, and 50 mg (Dainippon Sumitomo Pharma Co., Ltd.) and others
Tanatril Tablets 2.5, 5, and 10 (Tanabe Seiyaku Co., Ltd.)
Renivace Tablets-2.5, 5, and 10 (Banyu Pharmaceutical Co., Ltd.) and others
Captoril Fine Granules, Captoril Tablets 12.5 mg and 25 mg, Captoril-R (Sankyo Co., Ltd.) and others
Conan Tablets 5 mg, 10 mg, and 20 mg (Mitsubishi Pharma Corporation) and others
Inhibace Tablets 0.25, 0.5, and 1 (Chugai Pharmaceutical Co., Ltd.) and others
Acecol Tablets 1 mg, 2 mg, and 4 mg (Sankyo Co., Ltd.)
Adecut 7.5 mg., 15 mg., and 30 mg. Tablets (Takeda Pharmaceutical Company Limited) and others
Odric Tablet 0.5 mg and 1 mg (Sanofi-Aventis K.K.), Preran 0.5 mg and 1 mg Tablets (Chugai Pharmaceutical Co., Ltd.) and others
Cibacen Tablets 2.5 mg, 5 mg, and 10 mg (Novartis Pharma K.K.) and others
Coversyl Tablets 2 mg and 4 mg (Daiichi Pharmaceutical Co., Ltd.) and others
Zestril Tablets 5, 10, and 20 (AstraZeneca K.K.), Longes Tablets 5 mg, 10 mg, and 20 mg (Shionogi & Co., Ltd.) and others

[Use in pregnant, parturient, nursing women] This drug must not be administered to pregnant or possibly pregnant women. [Oligohydramnios, fetal or neonatal death, neonatal hypotension, renal failure, hyperpotassemia, cranial hypoplasia, and extremity contracture or craniofacial deformities ascribed to oligohydramnios have been reported in hypertensive patients who were administered angiotension converting enzyme inhibitors during the second and third trimesters of pregnancy. Furthermore, it has been reported from an overseas retrospective epidemiological survey that infants with only first trimester exposure to ACE inhibitors had an increased risk of congenital malformations as compared with infants who had no exposure to antihypertensive medications.]

<Reference Information> Company report

<Purgatives, clysters>

6 Sodium Picosulfate (drug product without the indication for bowel preparation before colon examination)

[Brand Name] Laxoberon Tablet (Teijin Pharma Limited) and others

[Contraindications]

Patients with suspected acute abdomen
Patients with a history of hypersensitivity to any components of this drug

<Reference Information> Company report

<Epidermides-Miscellaneous>

7 Tacalcitol (2 μg/g)

[Brand Name] Bonalfa Ointment 2 μg/g, Bonalfa Cream 2 μg/g, Bonalfa Lotion 2μg/g (Teijin Pharma Limited) and others

[Important Precautions] This drug is active vitamin D_3 preparations, thus concomitant use with analogue drug (active Vitamin D_3 topical product) or high-dose usage of this Product may increase serum calcium level. Since hypercalcaemia may reduce renal function, attention should be given to serum calcium, urine calcium and renal function (creatinine, BUN, etc.), and the patient's condition should be carefully monitored.

<Reference Information> Company report

<Epidermides-Miscellaneous>

8 Tacalcitol (2 μg/g)

[Brand Name] Bonalfa High Ointment 20 μg/g, Bonalfa High Lotion 20 μg/g (Teijin Pharma Limited)

[Important Precautions] Since this drug is active vitamin D_3 preparations, usage of this Product may cause serum calcium level to increase. Because hypercalcaemia may reduce renal function, when this Product is used in any of the following patients, tests on serum calcium, urine calcium, and renal function (creatinine, BUN, etc.) should be performed periodically (once after 2 to 4 weeks of the initial administration, and when needed by physician's judgment afterward). If any abnormality in these test results is observed, administration of this Product should be discontinued, and patient's condition should be monitored.

- Patients who use nearly 10g/day for widespread eruption, etc., and those who may have increased percutaneous absorption due to reduced skin barrier ability because of high severity of eruption.
- Patients with renal dysfunction
- Patients who are administrated any drug with suspicion of interaction with this Product, and those who had been treated with Cyclosporine before the initiation of this product.

[Adverse Reactions (clinically significant adverse reactions)] **Hypercalcaemia:** Hypercalcaemia and related symptoms (malaise, anorexia, etc.) may occur. If any abnormality is observed, administration of this product should be discontinued, and biochemical tests (serum calcium, urine calcium, etc.) should be conducted. Necessary measures such as fluid infusion should be taken.

<Reference Information> Company report

9 <Antituberculosis> Isoniazid

[Brand Name] Iscotin Powder 100%, Iscotin Tablets 50 mg and 100 mg, Iscotin Injection (Daiichi Pharmaceutical Co., Ltd.) and other

[Adverse Reactions (clinically significant adverse reactions)] Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), erythroderma (dermatitis exfoliative)

<Reference Information> Company report

10 <Antituberculosis> Isoniazid Sodium Methanesulfonate

[Brand Name] Neoiscotin, Neoiscotin Tablets (Daiichi Pharmaceutical Co., Ltd.)

[Clinically significant adverse reactions (similar drugs)] Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), erythroderma (dermatitis exfoliative)

<Reference Information> Company report

11 <Antivirals> Lamivudine (100 mg)

[Brand Name] Zefix Tablets 100 (GlaxoSmithKline K.K.)

[Adverse Reactions (clinically significant adverse reactions)] Rhabdomyolysis may occur. If symptoms such as myalgia, feelings of weakness, CK (CPK) increased and blood or urine myoglobin increased are observed, appropriate measures, such as discontinuation of administration, should be taken.

<Reference Information> Company report

12 <Human blood preparations> Freeze-dried Human Fibrinogen

[Brand Name] Fibrinogen HT-Wf (Benesis Corporation)

[Adverse Reactions (clinically significant adverse reactions)] **Thromboembolism:** Thromboembolism (deep vein thrombosis, thrombosis mesenteric vessel, pulmonary embolism, etc.) may occur. Patients should be carefully monitored, through blood tests for blood fibrinogen, platelet count, coagulability (prothrombin time etc.) etc., and if abnormalities are observed, appropriate measures should be taken.

<Reference Information> Company report

13 Over the counter drugs Containing Aspirin Containing Aspirin Aluminum

[Brand Name] Bufferin A, Bufferin Plus (Lion Corporation) and others

[When not to use the product] The following type of people must not take this product
Pregnant women who are expecting within 12 weeks.

<Reference Information> Company report

14 Over the counter drugs
Containing Aspirin And Not Containing Acetaminophen
Containing Aspirin Aluminum And Not Containing Acetaminophen

[Brand Name] Bayer Aspirin, Bayer Aspirin 100 (Bayer Yakuhin, Ltd.) and others
Ringl for Toothache (Sato Pharmaceutical Co., Ltd.) and others

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.

If the following symptoms are observed after taking this drug

In rare instances, the following serious symptoms may occur. Visit a physician immediately in such cases.

Hepatic function disorder: general malaise, jaundice (skin and white of the eyes become yellow) etc. may occur.

<Reference Information> Company report

3

List of products subject to Early Post-marketing Phase Vigilance

(As of August 1, 2006)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Zanamivir Hydrate / Relenza[*1]	GlaxoSmithKline K.K.	February 17, 2006
Baclofen / Intrathecal Gabalon 0.005%, 0.05%, and 0.2%	Daiichi Pharmaceutical Co., Ltd.	April 1, 2006
Interferon Beta / Feron[*2]	Toray Industries, Inc.	April 20, 2006
Epoetin Beta (Genetical recombination) / Epogin Injection Ampoule 750, 1500, and 3000, Epogin Injection Syringe 750, 1500, and 3000[*3]	Chugai Pharmaceutical Co., Ltd.	April 20, 2006
Somatropin (Genetical recombination) / Humatrope C 6 mg and 12 mg[*4]	Eli Lilly Japan K.K.	April 20, 2006
Zoledronic Acid Hydrate / Zometa Injection 4 mg[*5]	Novartis Pharma K.K.	April 20, 2006
Micafungin Sodium / Funguard 50 mg and 75 mg for Infusion[*6]	Astellas Pharma Inc.	April 20, 2006
Linezolid / Zyvox Tablets 600 mg, Zyvox Injection 600 mg[*7]	Pfizer Japan Inc.	April 20, 2006
Tosufloxacin Tosilate / Tosuflo Ophthalmic Solution 0.3%	Nidek Co., Ltd.	April 28, 2006
Clopidogrel Sulfate / Plavix Tablets 25 mg and 75 mg	Sanofi-Aventis K.K.	May 8, 2006
Silodosin / Urief Cap. 2 mg and 4 mg	Kissei Pharmaceutical Co., Ltd.	May 11, 2006
Tosufloxacin Tosilate / Ozex Ophthalmic Solution 0.3%	Toyama Chemical Co., Ltd.	May 11, 2006
Follitropin Alfa (Genetical recombination) / Gonalef for S.C. Injection 75 and 150	Serono Japan Co., Ltd.	May 11, 2006
Letrozole / Femara Tablets 2.5 mg	Novartis Pharma K.K.	May 11, 2006
Loxoprofen Sodium / Loxonin PAP 100 mg	Lead Chemical Co., Ltd.	May 23, 2006
Aripiprazole / Abilify Tablets 3 mg and 6 mg, Abilify Powder 1%	Otsuka Pharmaceutical Co., Ltd.	June 8, 2006
Solifenacin Succinate / Vesicare Tablets 2.5 mg and 5 mg	Astellas Pharma Inc.	June 8, 2006
Tolterodine Tartrate / Detrusitol Capsules 2 mg and 4 mg	Pfizer Japan Inc.	June 8, 2006

Amphotericin B AmBisome for Intravenous Infusion 50 mg	Dainippon Sumitomo Pharma Co., Ltd.	June 20, 2006
Magnesium Sulfate/Glucose Magsent Injection 100 mL	Toa Pharmaceuticals Co., Ltd.	June 20, 2006
Sertraline Hydrochloride Jzoloft Tablets 25 mg and 50 mg	Pfizer Japan Inc.	July 7, 2006
Somatropin (Genetical recombination) Genotropin 5.3 mg, Genotropin Inj. 12 mg, Genotropin MiniQuick s.c. Inj. 0.6 mg, 1.0 mg, and 1.4 mg[*8]	Pfizer Japan Inc.	July 26, 2006

Note) Subject to additional indication etc.

*1: An additional administration for "pediatrics"

*2: An additional indication for "improvement of viraemia in compensated cirrhosis type C (except in the patients with HCV serogroup 1 and high blood HCV-RNA load)"

*3: An additional indication for "anaemia of prematurity"

*4: An additional indication for "adult growth hormone hyposecretion (for severe cases only)"

*5: An additional indication for "bone lesions due to multiple myeloma and solid tumor metastases to bone"

*6: An additional administration for "pediatrics"

*7: An additional indication for "<Susceptible strains> methicillin-resistant Staphylococcus aureus (MRSA) sensitive to this drug <Indications> sepsis, deep skin infection, chronic pyoderma, secondary infection such as from traumatic injury/fever and surgical wound, and pneumonia"

*8: An additional indication for "adult growth hormone hyposecretion (for severe cases only)"

Reference Material

Pediatric Guidelines for Treatment and Management of Asthma

Attached for your information is the "Pediatric Guidelines for Treatment and Management of Asthma", which was developed as one of the projects to promote proper use of pharmaceuticals etc. in FY2005.

You can also access to the guideline, including the reference materials available on MHLW website (http://www.mhlw.go.jp/)

Pediatric Guidelines for Treatment and Management of Asthma

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Research in 2005

I. Treatment of acute childhood asthma exacerbations at medical institutions

It is important to distinguish level of exacerbations in order to conduct appropriate treatment of childhood asthma. Table 1 shows the criteria to distinguish mild, moderate and severe exacerbations, as well as respiration failure.

Table 1. Assessment the severity of childhood asthma exacerbations

		Mild exacerbation	Moderate exacerbation	Severe exacerbation	Respiratory failure
Respiratory condition	**Wheezing**	Mild	Distinct	Marked	Reduced/ disappeared
	Retractive breathing	None to mild	Distinct	Marked	Marked
	Prolonged expiration	None	Present	Distinct	Marked
	Orthopnoea	Can lie down	Prefers sitting	Bending forward	Present
	Cyanosis	None	None	Possible	Present
Respiratory rate		Slight increase	Increase	Increase	Indefinite
Target normal respiratory rate when waking (/minute) Less than 2 months: <60, 2 to 12 months: <50, aged 1 to 5: <40, aged 6 to 8: <30					
Pulse rate (/minute)					
Paradoxical pulse					
Dyspnoea (feeling)	**When resting**	None	Present	Marked	Marked
	When walking	Mild	Marked	Difficulty in walking	Abasia
Lifestyle conditions	**Way of speaking**	Takes breath between sentences	Takes breath between phrases	Takes breath between words	Unable to speak
	Way of eating	Nearly normal	Somewhat difficult	Difficult	Unable
	Sleeping	Normal	Awakening	Disordered	
Consciousness disturbed (conditions)	**State of excitement**	Normal	Somewhat excited	Excitement	Confusion
	Consciousness decreased	None	None	Somewhat present	Present
PEF	**Before inhalation**	＞60%	30～60%	＜30%	Unmeasurable
	After inhalation	＞80%	50～80%	＜50%	Unmeasurable
Spo_2 (%, room air)		≤96%	92～95%	≤91%	＜91%
Pao_2 (mmHg)					
$Paco_2$ (mmHg)		＜41	＜41	41～60	＞60

In addition, since signs of severe exacerbations in infants are quite different from those in older children, precaution is required (Table 2).

Table 2. Symptoms of severe asthma exacerbations in infants

1 Severe cough (vomiting may occur)
2 Marked wheezing (sometimes reduced)
3 Retraction of suprasternal space, supraclavicular fossa, space between the ribs
4 Tachypnoea
5 Nasal alar breathing
6 Seesaw breathing
7 More comfortable to be held (orthopnoea)
8 Failing to sleep (or unable to sleep)
9 Cyanosis
10 Moaning
11 Tachycardia
12 In a bad mood
13 Crying out (excitement)
14 Depressed level of consciousness

1. Treatment of exacerbations in infants (under age of 2)

The following treatments shown in Table 3 are carried out for infants.

Table 3. Management of asthma exacerbations in infants at medical institutions (for under age of 2)

Type	Mild exacerbation	Moderate exacerbation	Severe exacerbation	Respiratory failure
Primary treatment	β_2-agonist inhalation	β_2-agonist inhalation (repeatable[*1]) Oxygen inhalation (Spo_2 $<$95%)	Hospitalization Repeated β_2-agonist inhalation[*1] Oxygen inhalation Infusion corticosteroid i.v.[*2]	Hospitalization Continuous Isoproterenol inhalation[*3] Oxygen inhalation Infusion Repeated corticosteroid i.v.[*4]
Additional treatment	Repeated β_2-agonist inhalation[*1]	(principally hospitalized) Administration of corticosteroid[*2] (i.v. injection/oral) Infusion Aminophylline continuous drip infusion (consideration)[*5]	Isoproterenol continuous inhalation[*3] Repeated corticosteroid i.v.[*4] Aminophylline continuous drip infusion (consideration)[*5]	Intratracheal intubation Artificial respiration control Aminophylline continuous drip infusion (consideration)[*5] Anesthetics (consideration)

For exacerbations in patients who are receiving treatment of step 3 or higher through long-term management, consider treatment that is one step higher.

[Precautions]

∗1 Assess the efficacy of β_2-agonist at 15 to 30 minutes after inhalation; Repeated inhalation is possible up to 3 times in intervals of 20 to 30 minutes. For severe exacerbation or severer exacerbations, carry out inhalation on an as-needed basis if necessary.

∗2 Corticosteroids should be administered intravenously over approximately 10 minutes or as a continuous intravenous infusion over approximately 30 minutes, or as oral drugs. Fundamentally, this is a treatment where the infant is hospitalized. Administration of systemic corticosteroids without careful consideration is not recommended. Use such drugs for approximately 3 days per month, and a few times per year.
If more frequent administration is necessary, refer the patient to a specialist in pediatric allergies.

∗3 Continuous Isoproterenol inhalation should be performed. In facilities where this treatment is difficult or impossible, β_2-agonist inhalation should be repeated.

∗4 Depending on the symptoms, use 5 mg/kg of hydrocortisone every 6 to 8 hours, or 0.5 to 1 mg/kg of prednisolone or methylprednisolone every 6 to 12 hours.

∗5 Make sure not to overdose. In principle, administration is not recommended for infants under 6 months old, or for those with convulsive disorders.
With regard to use when the patient develops pyrexia, careful consideration should be made for the properness.
It is recommended that this treatment should be carried out by a physician who has sufficient knowledge about treatment for pediatric asthma.

The key points are as follows.

∗1 As the inhaled β_2-agonist, ① salbutamol (Venetlin®), ② procaterol (Meptin®), or ③ isoproterenol (Asthpul®) is used.

① Since Venetlin® comes in a 0.5% 30 mL vial, use a pipette to place 0.1 to 0.3 mL in a nebulizer, add 2 mL of physiological saline, and inhale it with a compressor.

② The same applies for Meptin®, but since an inhalation method unit of 0.3 mL/1 time has been released, it has become easier to use. This drug has little cardiac stimulation effect, but tremors may develop easily. Rather, this adverse reaction serves as a brake to prevent excessive inhalation.

③ For Asthpul®, 0.5% 50 mL is used. Compared to the other 2 drugs, the disadvantage of this drug is that it has a strong cardiac stimulation effect, and causes the pulse to increase easily. On the contrary, since it has a shot duration of effect and a rapid onset of bronchodilation effect, it is possible to adjust the inhalation amount using the pulse rate as an indicator. This is a major reason why continuous isoproterenol inhalation is used in Japan.

For inhalation devices, electric compressors are used. Ultrasonic nebulizers are not recommended since cough may develop easily due to small particle size as well as inherent changes in the concentration of the residual liquid.

There are also methods that use pressurized metered dose inhalers (pMDI) and nebulizers with masks, which use salbutamol (Sultanol®, Airomir®), procaterol (Meptin Kid Air®), etc.

∗2 As intravenous corticosteroids, prednisolone (Predonine®), methylprednisolone (Solu-medrol®) and hydrocortisone (Saxizon®, Solu-cortef®) are used, and as oral administration, prednisolone (Predonine®), betamethasone (Rinderon®) and dexamethasone (Decadron®) are used.

1-shot intravenous injections and intravenous drip infusions are performed. However, although in extremely rare cases, children may have allergies to drugs, therefore it is recommended to perform intravenous drip infusions when administering these drugs for the first time.

Basically, short-acting preparations are preferable for oral drugs, but since prednisolone only comes in tablet form and powder form and has a strong, bitter taste, it is difficult to administer to infants.

Although it is inevitable to use Dexamethasone Elixir and Betamethasone Syrup, caution should be exercised against adverse reactions.

∗3 Although continuous intravenous infusion of isoproterenol is used commonly in children in Japan, it is recommended to conduct this at a specialized hospital since it has a strong cardiac stimulation effect. Infusion should be carefully conducted using a pulse oximeter, cardiograph monitoring and oxygen inhalation concomitantly. Please refer to Table 4 for details.

∗5 Since there have been reports of adverse reactions associated with overdoses of this drug, if using this drug in infants with convulsive disorder or those who are under 6 months old, it is preferable to administer this drug to such children under the guidance of a physician who has sufficient knowledge about treatment of pediatric asthma. Caution should be exercised when using this drug to patients who develops pyrexia.

Table 4. Key points regarding isoproterenol continuous inhalation

1. Preparation of solution
   Asthpul® (0.5%) 2 to 5 mL + physiological saline 500 mL
   (Possible to increase amount for ineffective cases or respiration failure: For example, start with Asthpul® (0.5%) 10 mL + physiological saline 500 mL)
   * Use of Proternol-L® Inj. (0.2 mg/1 mL, 1 mg/5 mL) as an inhaled drug is an off label use (not covered by the health insurance)
2. Connection to nebulizer
   Dispense the prepared solution into Inspiron® or a giant nebulizer.
   Fix the face mask that is connected to the nebulizer so that it covers the patient's mouth and nose, but for infants and patients who resist the mask, place the patient inside an oxygen tent and spray into the tent.
3. Method
   1) Start with an oxygen concentration of 50% and spray rate of 10 L/minute.
   2) This treatment lacks quantitative indicators for drugs. Therefore, monitor the severity of exacerbations and the development of adverse reactions in a detailed manner, and adjust the concentration of the solution and the spray amount as appropriate to optimize the spray amount.
   3) Determine approximate usage amount of the solution based on the decrease per time.
   4) Maintain Spo_2 at 95% or higher.
   5) Implement inhalation from several hours to several days, depending on the severity of the exacerbation.
   6) If performing continuous inhalation by increasing the amount of isoproterenol, decrease the concentration of isoproterenol to a usual level first after symptoms improve.
   7) After improvements in symptoms are observed, gradually discontinue administration by tapering the spray amount or lowering the concentration of the solution. Afterwards, switch to the intermittent inhalation of β_2 agonist.
4. Monitoring
   1) Pulse oximeter, heart rate, respiratory rate, and electrocardiogram: Must be carried out continuously.

2) Serum electrolyte, cardiac enzymes, blood pressure: As appropriate
3) In cases with increased $Paco_2$, blood gas analysis can be conducted easily by placing an arterial catheter.

5. Efficacy assessment
1) Clinical symptoms such as wheezing, retractive breathing, cyanosis.
2) When the efficacy of inhalation starts becoming evident, it is often the case that the heart rate, which had been increased, decreases.
3) If Spo_2 does not increase even if sufficient spraying is performed, or if the heart rate does not decrease even if Spo_2 is 95% or higher, it is possible that efficacy is insufficient. In such cases, perform a blood gas analysis and chest X-ray, reassess the respiratory condition and check for complications.

6. Precautions
1) It should be reminded that it becomes difficult to monitor the patient's condition due to an aerosol mist when spraying inside an oxygen tent.
2) Encourage patients to produce sputum, change in body position, and move their body at regular time intervals.
3) Regularly check the attachment condition of the face mask.
4) Always pay attention to obstruction of the tube (folding and bending, accumulation of fluid, compression, etc.) and the condition of the spray. In particular, if physiological saline is used with Inspiron®, the tube may easily become clogged.
5) If findings suggesting myocardial disorder such as electrocardiogram changes and chest pain are observed, consider reducing the amount of isoproterenol as quickly as possible, and at the same time, test cardiac enzymes.
6) If symptoms became aggravated and there is lack of response even if the amount of isoproterenol is increased, proceed with preparing a system where artificial respirator control is possible.

2. Drug therapy during exacerbations in infants and older children

The plan for infants and older children aged 2 to 15 is shown in Table 5.

Table 5. Drug therapy plan for asthma exacerbations at medical institutions (for aged 2 to 15)

2 to 15 years old				
Type	**Mild exacerbation**	**Moderate exacerbation**	**Severe exacerbation**	**Respiratory failure**
Primary treatment	β_2-agonist inhalation	Repeated β_2-agonist inhalation*1 Oxygen inhalation (consider at Spo_2 <95%)	Hospitalization Repeated β_2-agonist inhalation *1 Corticosteroid i.v.*2 Aminophylline continuous drip infusion*3	Hospitalization Isoproterenol continuous inhalation*4 Oxygen inhalation, infusion Repeated corticosteroid i.v. *2 Aminophylline continuous drip infusion*3
Additional treatment	Repeated β_2-agonist inhalation *1	Administration of corticosteroid (i.v. injection/oral administration)*2 and/or Aminophylline i.v. drip infusion • Continuous drip infusion*3 Monitor response to the above treatment, and consider treatment through hospitalization if there is lack of response	Isoproterenol continuous inhalation*4 Repeated corticosteroid i.v. *2	Isoproterenol continuous inhalation (consider increase in isoproterenol)*4 Correction of acidosis Intratracheal intubation Artificial respiration control Anesthetics (consideration)

- For cases who repeat attacks, review the cause of the attacks, give guidance regarding an appropriate lifestyle, and reconsider controller medications
- Frequent use or continuous systemic administration of corticosteroids may cause adverse reactions. Administration should be discontinued within a short time, and it is important not to administer corticosteroids

irresponsibly. If necessary, refer the patient to a specialist in pediatric allergies.
- It is recommended for aminophylline treatment in infants to be carried out by a physician who has sufficient knowledge about treatment for pediatric asthma.

∗1 Assess the efficacy of β_2-agonist 15 to 30 minutes after inhalation; repeated inhalation is possible up to 3 times in intervals of 20 to 30 minutes.
For patients of this age group, pMDI is sufficient for much of β_2-agonist inhalation. For infants, however spacers with masks are more certain.

∗2 Administration of systemic corticosteroids:
Intravenous injection: Hydrocortisone 5 to 7 mg/kg, every 6 hours; start with prednisolone, 1 to 1.5 mg/kg, 0.5 mg/kg every 6 hours afterwards; or methylprednisolone 1 to 1.5 mg/kg every 4 to 6 hours.
Perform intravenous injection over approximately 10 minutes, or perform drip infusion over 30 minutes.
Internal use: Prednisolone 0.5 to 1 mg/kg/day (3 times a day). If oral administration of prednisolone is difficult, administer Betamethasone Syrup or Dexamethasone Elixir 0.05 mg (0.5 mL)/kg/day (twice a day).
Corticosteroids are also used at the age at which oral use of Predonine is possible. In addition, since aspirin asthma and corticosteroid hypersensitivity are known to occur rarely in junior high school children or older children, intravenous drip infusion is fundamental when using succinate ester corticosteroids (Solu-cortef®, Saxizon®, Predonine®, Solu-medrol®, etc.).

∗3 Aminophylline intravenous drip infusion: Carry out for at least 30 minutes.
Aminophylline continuous drip infusion: Blood theophylline concentration: 8 to 15 μg/mL
For aminophylline intravenous drip infusion, adhere to the dosage appropriately. However, caution should be exercised when using in infants aged 2 to 5 with pyrexia.

∗4 Isoproterenol continuous inhalation: Asthpul® (0.5%) 2 to 5 mL or Proternol-L® Inj. 10 to 25 mL + physiological saline 500 mL. If ineffective or if there is respiratory failure, it is possible to increase the amount [for example, start from Asthpul® (0.5%) 10 mL + physiological saline 500 mL].

The initial dose and maintenance dose of aminophylline when theophylline products have not been orally administered previously are as shown in Table 6. In addition, precautions for use in infants is shown in Table 7.

Table 6. Standards of doses for aminophylline when asthma attacks in children

Age	Dose	
	Initial dose (mg/kg)	Maintenance dose (mg/kg/h)
Under age of 1	3~4	0.4
Under age of 1~2	3~4	0.8
2~15	4~5	0.8
15~	4~5	0.6

(When patients do not develop pyrexia and have not been orally administered with theophylline products)

Table 7 Precautions relating to use of aminophylline injection drugs during asthma attacks in infants

- If β_2-agonists and corticosteroids have insufficient efficacy for severe attack and respiratory failure, it is recommended to consider use of aminophylline injection drugs by a physician who has sufficient knowledge relating to theophylline drugs.
- Use of aminophylline injection drugs is not recommended, in principle, for patients with convulsive diseases such as febrile convulsion and epilepsy.
- Caution should be excised when using the drug in patients with pyrexia.
- Establish blood concentration approximately at 10 μg/mL, and monitor the blood concentration as necessary. Adjust the dose to a maximum of approximately 15 μg/mL as necessary.
- Theophylline clearance may decrease due to pyrexia, viral infections, food, concomitant drugs, etc., and the blood concentration may increase.

The number of sprays per pMDI is as shown in Table 8. It is important to confirm the residual amount.

Table 8. List of metered-dose inhalation drugs

Short-acting inhaled β_2-agonists

Product name	Manufacturer name	Number of sprays (as described in package insert)
Sultanol Inhaler	GlaxoSmithKline K.K.	Approx. 200 times
Meptin Air 10 μg	Otsuka Pharmaceutical Co., Ltd.	Approx. 100 times
Meptin Kid Air 5 μg	Otsuka Pharmaceutical Co., Ltd.	Approx. 100 times
Berotec Metered Aerosol 100	Nippon Boehringer Ingelheim Co., Ltd.	Approx. 200 times
Airomir	Dainippon Sumitomo Pharma Co., Ltd.	Approx. 200 times

Inhaled corticosteroids

Flutide 50 Air	GlaxoSmithKline K.K.	120 times
Flutide 100 Air	GlaxoSmithKline K.K.	60 times
Qvar	Dainippon Sumitomo Pharma Co., Ltd. Schering-Plough K.K.	100 times

Antiallergic drugs

Intal Aerosol A	Astellas Pharma Inc.	Approx. 200 times

Ⅱ. Drug therapy in long-term management of childhood asthma

In long-term management, accurately comprehending the severity is a major premise.
The severity of asthma in JPGL2005 is as shown in Table 9.

Table 9. Severity of asthma based on clinical symptoms before treatment

Component of severity	Degree and frequency of symptoms
Intermittent	• Seasonal cough and mild wheezing develop a few times per year. • May sometimes be accompanied by dyspnoea, but symptoms improve in a short period of time with a single use of a β_2-agonist on an as needed basis, and do not persist.
Mild persistent	• Cough and mild wheezing develop at least once a month, and less than once a week. • May sometimes be accompanied by dyspnoea, but duration of persistence is short and there are little cases where daily activities are disturbed.
Moderate persistent	• Cough and mild wheezing develop at least once a week. Does not persist everyday. • May sometimes develop to moderate/severe exacerbation, and daily activities are disturbed.
Severe persistent	• Cough and mild wheezing persist everyday. • Develop to moderate/severe exacerbation once or twice a week, and daily activities and sleeping are disturbed.
Severe persistent asthma (intractable/most severe)	• Even when treatment equivalent to that for severe persistent asthma is conducted, symptoms equivalent or greater than those of moderate persistent asthma persist. • May frequently receive after-hours consultation in the nighttime due to moderate/severe exacerbation, undergo repeated hospitalization, and have restrictions in daily activities.

In the case of ultimate assessment severity, the 4 stages of the treatment steps described below should be given consideration (Table 10). This is because, for example, if considering cases where a patient takes 400 μg/day of an inhaled corticosteroid and symptoms were almost completely controlled, it is often the case the patient himself/herself and those around the patient mistakenly believe that the patient has a mild case of asthma, resulting in the patient neglecting everyday life management as well as the medication plan, which then leads to acute aggravation. These kinds of cases should be handled as "severe persistent asthma" even if there are almost no symptoms.

Table 10. Assessment of severity of asthma by considering current treatment steps

	Current treatment steps			
Patient's symptoms/frequency	**Step 1**	**Step 2**	**Step 3**	**Step 4**
Intermittent • Seasonal cough and mild wheezing develop a few times per year • May sometimes be accompanied by dyspnoea, but symptoms improve in a short period of time with a singe use of a β_2-agonist on an as needed basis, and do not persist	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Mild persistent • Cough and mild wheezing develop at least once a month, and less than once a week. • May sometimes be accompanied by dyspnoea, but duration of persistence is short and there are little cases where daily activities are disturbed	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Moderate persistent • Cough and mild wheezing develop at least once a week. Does not persist everyday. • May sometimes develop to moderate/severe exacerbation, and daily activities and sleeping are disturbed	Moderate persistent	Severe persistent	Severe persistent	Severe persistent (Intractable/most severe)
Severe persistent • Cough and mild wheezing persist everyday • Develop to moderate/severe exacerbation once or twice a week, and daily activities and sleeping are disturbed	Severe persistent	Severe persistent	Severe persistent	Severe persistent (Intractable/most severe)

1. Drug therapy in long-term management for infants (under age of 2)

The plan for infants is as shown in Table 11. It is the primary therapy to perform supportive care for the intermittent asthma (step 1), antiallergic drugs that contain DSCG (disodium cromoglycate) and LTRA (leukotriene receptor antagonist) for mild persistent asthma (step 2), 100 μg/day of inhaled corticosteroids (inhaled corticocorticosteroid ICS) for moderate persistent asthma (step 3), and concomitant use of 150 to 200 μg/day of ICS with LTRA and (or) DSCG for severe persistent asthma (step 4). The points that should be considered when using theophylline sustained release products are shown in Table 12.

Table 11. Drug therapy for long-term management of asthma in infants

	Step 1 **Intermittent asthma**	**Step 2** **Mild persistent asthma**	**Step 3** **Moderate persistent asthma*7**	**Step 4** **Severe persistent asthma*7**
Basic treatment	None (Perform treatment for acute exacerbations depending on the severity of the exacerbation)	Antiallergic drugs*1	Inhaled corticosteroids*4 (100 μg/day)	Inhaled corticosteroids*4 (150 to 200 μg/day) One or combination of the following: • Leukotriene receptor antagonist • DSCG inhalation*3 (2 to 4 times/day)

Additional treatment	Antiallergic drugs*1	DSCG inhalation*2, *3 Inhaled corticosteroid*4 (50 μg/day)	One or a combination of the following: • Leukotriene receptor antagonist • DSCG inhalation*3 (2 to 4 times/day) • β_2-agonist (patch application before bedtime or oral administration twice/day)*5 • Theophylline sustained release product (consideration)*6 (Blood concentration 5 to 10 μg/mL)	• β_2-agonist (patch application before bedtime or oral administration twice/day)*5 • Theophylline sustained release product (consideration)*6 (Blood concentration 5 to 10 μg/mL)

∗1 Oral antiallergic drugs: Leukotriene receptor antagonist, histamine H_1 antagonist, Th_2 cytokine inhibitor, chemical mediator release inhibitor. Inhalable antiallergic drugs: DSCG solutions.

∗2 When using oral antiallergic drugs.

∗3 Solutions are inhaled using a nebulizer. Inhale concurrently with a small amount (0.05 to 0.1 mL) of a β_2-agonist as necessary. Fundamentally, β_2-agonists should be discontinued after the exacerbation is controlled.
For DSCG inhalation, the solutions that are currently commercially available are isotonic solutions and induction of cough is decreased. When starting treatment, compliance is better if inhalation is carried out after mixing a small amount (0.05 to 0.1 mL) of a β_2-agonist (Venetlin® or Meptin®).
After stabilization, leave out the β_2-agonist.

∗4 For BDP-pMDI and FP-pMDI, carry out inhalation by using an inhalation aid with a mask.
For ICS, if a mask with a spacer is used, Flutide Air® and Qvar® can be sufficiently used.
In 2006, Pulmicort Respules is expected to be launched and will be available as a drug of this class, but its strength is different and the dosage differs from BDP and FP. A jet-type nebulizer will be used as the inhalation device. Future consideration is necessary to review whether to use mesh-type nebulizers.

∗5 It is fundamental for β_2-agonists (patch, oral) to be discontinued after symptoms are controlled.
Adhesive preparations of β_2-agonists are used frequently. Since safety is currently not established as a controller medication for long-term use, it is necessary to concomitantly use anti-inflammatory agents, particularly ICS, when using it for a long period of time, similar to the precautions for the long-acting inhalaed β_2-agonist salmeterol.

∗6 In principle, this does not apply to children who are under age of 6 months. Careful consideration should be made when using in such children; in principle, this product is not recommended for children with convulsive diseases. It is preferable to give instructions beforehand whether temporally dose reduction or discontinuation of administration will be necessary when pyrexia develops.

∗7 It is preferable for treatment in step 3 or higher to be performed under the guidance and control of a specialist in pediatric allergies. In principle, treatment of patients with insufficient control of asthma with step 4 treatment should be performed by a specialist.

Table 12. Significance and points to consider for regular oral administration of theophylline sustained release products in long-term management of asthma in infants

- An additional treatment that is given consideration for patients with moderate persistent asthma (step 3) or more severe asthma
- In principle, long-term management using theophylline sustained release products is not applicable to children who are under age of 6 months
- In principle, even if a child is aged 6 months and older, this is not recommended for children with convulsive diseases such as epilepsy and febrile convulsion
- Precaution is necessary when administering to children with a family history of convulsive diseases
- It is preferable to give instructions beforehand if temporally dose reduction or discontinuation of administration will be necessary when pyrexia develops
- During administration of theophylline sustained release products, it is necessary to give sufficient precaution to concomitant use of drugs that suppress theophylline clearance and increase blood concentration (erythromycin, clarithromycin etc.)
- It has been reported that antiallergic drugs that show the transition into the central nervous system and primary exert histamine H_1 antagonistic effect lower convulsion thresholds. Caution might be exercised when coadministering such antiallergic drugs with theophylline sustained release products to infants with asthma
- Use of suppositories during regular oral administration is not recommended

2. Drug therapy for long-term management in infants

Treatment for infants aged 2 to 5 is shown in Table 13.

Treatment for the intermittent asthma (step 1) consists of symptomatic treatment, mild persistent asthma (step 2) consists of antiallergic drugs that contain DSCG and LTRA or 50 to 100 μg/day of ICS, moderate persistent asthma (step 3) consists of 100 to 150 μg/day of ICS, and severe persistent asthma consists of 150 to 300 μg/day of ICS, coadministered with either of LTRA, DSCG, theophylline sustained release product (SRT), or LABA (long acting β_2-agonist).

Table 13. Drug therapy plan for long-term management of childhood asthma (infants aged 2 to 5)

	Step 1 Intermittent asthma	Step 2 Mild persistent	Step 3 Moderate persistent	Step 4 Severe persistent
Basic treatment	Drug therapy based on the type of asthmatic exacerbation	Antiallergic drugs*1, *5 or inhaled corticosteroid (consideration)*2 (50 to 100 (μ g/day)	Inhaled corticosteroid*2 (100 to 150 (μ g/day)	Inhaled corticosteroid*2, *4 (150 to 300 (μ g/day) One or a combination of the following: • Leukotriene receptor antagonist • DSCG*5, *6 • Theophylline sustained release product*3 • Long-acting inhaled β_2-agonist*7
Additional treatment	Antiallergic drugs*1	Theophylline sustained release product*3	One or a combination of the following • Leukotriene receptor antagonist • DSCG*5, *6 • Theophylline sustained release product*3 • β_2-agonist (patch application before bedtime or oral administration twice/day)*6 • Long-acting inhaled β_2-agonist*7	

∗1 Antiallergic drugs: Classified into chemical mediator release inhibitor, histamine H_1 antagonists, leukotriene receptor antagonists and Th_2 cytokine inhibitors. Includes DSCG and oral antiallergic drugs.
∗2 Inhaled corticosteroids: Strength is calculated based on conversion to FP (fluticasone propionate) or BDP (beclometasone dipropionate).
∗3 When using theophylline sustained release products, caution should be exercised against the development of adverse reactions accompanying increased blood concentration particularly when the patient develops pyrexia.
∗4 For patients whose symptoms cannot be controlled with step 4 treatment, carry out treatment that includes administration of oral corticosteroids under the control of a specialist.
∗5 If inhaling DSCG solution with a nebulizer, inhale concurrently with a small amount (0.05 to 0.1 mL) of a β_2-agonist as necessary.
∗6 Fundamentally, β_2-agonists should be discontinued after the exacerbation is controlled.
∗7 Children who can inhale DPI
When children become 4 or 5 years of age, they can inhale dry powder (DPI) of salmeterol (Serevent 25®), and it is permissible to use DPI but concomitant use with ICS is necessary.

3. Drug therapy for long-term management in older children (aged 6 to 15)

The plan for older children is shown in Table 14.

The major differences as compared to infants is that in step 2, ICS is ranked higher than antiallergic drugs, and in steps 3 and 4, inhaled LABA became ranked higher than before as concomitant medications.

Table 14. Drug therapy plan for long-term management of childhood asthma (older children aged 6 to 15)

	Step 1 Intermittent asthma	Step 2 Mild persistent asthma	Step 3 Moderate persistent asthma	Step 4 Severe persistent asthma
Basic treatment	Drug therapy based on the type of asthmatic exacerbation	Inhaled corticosteroid*2 (100 μg/day) or antiallergic drugs*1	Inhaled corticosteroid*2 (100 to 200 μg/day)	Inhaled corticosteroid*2, *3 (200 to 400 μg/day) One or combination of the following: • Leukotriene receptor antagonist • Theophylline sustained release product • Long-acting inhaled β_2-agonist • DSCG • β_2-agonist patch
Additional treatment	Antiallergic drugs*1	Theophylline sustained release product	One or combination of the following: • Leukotriene receptor antagonist • Theophylline sustained release product • Long-acting inhaled β_2-agonist • DSCG • β_2-agonist patch	Oral corticosteroid*3 (consideration to short-term/intermittent) Hospital treatment (consideration)

∗1 Antiallergic drugs: Classified into chemical mediator release inhibitor, histamine H_1 antagonists, leukotriene receptor antagonists and Th_2 cytokine inhibitors. Includes DSCG and oral antiallergic drugs.

∗2 Inhaled corticosteroid drugs: Strength Potency is calculated based on conversion to FP (fluticasone propionate) or BDP (beclometasone dipropionate).

∗3 For patients whose symptoms cannot be controlled with step 4 treatment, carry out treatment that includes administration of oral corticosteroids under supervision of a specialist