

Pharmaceuticals and Medical Devices Safety Information

No. 225 June 2006

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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).*

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. 224).

1 Azithromycin Hydrate

| | |
|---|--|
| Brand Name (name of company) | Zithromac Fine Granules for Pediatric Use, Zithromac Capsules for Pediatric Use 100 mg, Zithromac Tablets 250 mg and 600 mg (Pfizer Japan Inc.) |
| Therapeutic Category | Acting mainly on gram-positive bacteria and mycoplasma |
| Indications | <p>(Zithromac Fine Granules for Pediatric Use, Zithromac Capsules for Pediatric Use 100 mg)</p> <p><Susceptible strains> Azithromycin-susceptible <i>Staphylococcus sp.</i>, <i>Streptococcus sp.</i>, <i>Pneumococcus sp.</i>, <i>Moraxella (Branhamella) catarrhalis</i>, <i>Haemophilus influenzae</i>, <i>Chlamydia pneumoniae</i>, <i>Mycoplasma sp.</i></p> <p><Indications> Pharyngolaryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, lung abscess, otitis media (Zithromac Tablets 250 mg)</p> <p><Susceptible strains> Azithromycin-susceptible <i>Staphylococcus sp.</i>, <i>Streptococcus sp.</i>, <i>Pneumococcus sp.</i>, <i>Moraxella (Branhamella) catarrhalis</i>, <i>Haemophilus influenzae</i>, <i>Peptostreptococcus sp.</i>, <i>Chlamydia sp.</i>, <i>Mycoplasma sp.</i></p> <p><Indications> Deep skin infection, lymphangitis/lymphadenitis, pharyngolaryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, lung abscess, secondary infection of chronic respiratory lesion, urethritis, cervicitis, sinusitis, periodontal tissue inflammation, pericoronitis, jaw inflammation (Zithromac Tablets 600 mg)</p> <p><Susceptible strains> <i>Mycobacterium avium</i> complex (MAC)</p> <p><Indications> Suppression and treatment of disseminated <i>mycobacterium avium</i> complex (MAC) symptoms accompanying acquired immunodeficiency syndrome (AIDS)</p> |

<<PRECAUTIONS (underlined parts are additions)>>

**[Adverse Reactions
(clinically significant
adverse reactions)]**

Hepatitis, hepatic function disorder, jaundice: Hepatitis, hepatic function disorder, and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

White blood cell decreased, granulocytopenia, platelets decreased: White blood cell decreased, granulocytopenia, and platelets decreased may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored, and if myalgia, feelings of weakness, CK (CPK) increased, myoglobin blood increased and myoglobin urine increased is observed.

administration should be discontinued and appropriate measures should be taken. In addition, caution should be exercised against development of acute renal failure associated with rhabdomyolysis.

<Reference Information>

Number of reported adverse drug reaction cases in about the last 3 years (April 2003 to March 2006) (events for which a causality to the drug could not be denied)

- Hepatitis: 5 cases (no fatal case)
- White blood cell decreased, granulocytopenia, platelets decreased: 4 cases (no fatal case)
- Rhabdomyolysis: 5 cases (no fatal case)

The number of patients treated with Azithromycin for a year estimated by MAH (Marketing Authorisation Holder): approximately 30 million (FY 2005)
Marketed in Japan in: June 2000

Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions | Remarks |
|--|---------------------------|--------------------------------|-----------------------------------|--|----------------|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 1 | Female Under age of 10 | Acute pneumonia (none) | 300 mg 3 days | <p>Drug-induced hepatitis</p> <p>On day 1 of administration: The patient was diagnosed with pneumonia and hospitalized in the pediatric department. Treatment using this drug and flomoxef sodium was initiated.</p> <p>On day 3 of administration (last day of administration): Administration of this drug was completed.</p> <p>1 day after completion: Increase in AST (GOT), ALT (GPT), and LDH were confirmed.</p> <p>3 days after completion: Since pyrexia persisted and depressed level of consciousness developed, the patient was referred to pediatric department of a general hospital, and she was hospitalized. Treatment through intravenous injection of 20ml of glycyrrhizin/glycine/cysteine × 3 times and multivitamin products was initiated.</p> <p>11 days after completion: AST (GOT) and ALT (GPT) were improved, and CRP became nearly negative.</p> <p>25 days after completion: During clinical course, pyrexia was noted twice, but since hepatic function become normal, symptoms were considered to have improved and the patient was discharged.</p> <p>DLST test: this drug S.I. 185% (positive) flomoxef sodium S.I. 133% (negative)</p> <p>Cytomegalovirus: negative EB (Epstein-Barr) virus: negative</p> | Company report |
| Concomitant medications: flomoxef sodium | | | | | |

Clinical Laboratory Values

| | On day 1 of administration | 1 day after completion | 3 days after completion | 4 days after completion | 5 days after completion | 7 days after completion | 11 days after completion | 23 days after completion |
|-------------------------|----------------------------|------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------|--------------------------|
| AST (GOT) (IU/L) | 26 | 102 | 2480 | 1960 | 818 | 179 | 31 | 20 |
| ALT (GPT) (IU/L) | 11 | 42 | 1614 | 1663 | 1394 | 747 | 183 | 18 |
| Al-P (IU/L) | -- | -- | -- | -- | 263 | 302 | 468 | -- |
| LDH (IU/L) | 203 | 839 | 5671 | 4670 | 2415 | 1164 | 755 | 478 |
| γ-GTP (IU/L) | -- | -- | 22 | 24 | 41 | 81 | 101 | 70 |
| Total bilirubin (mg/dL) | -- | -- | -- | 0.4 | 0.5 | 0.5 | -- | 0.3 |
| CRP (mg/dL) | 5.0 | -- | 0.95 | 0.63 | 0.31 | 0.18 | 0.04 | 0.29 |

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

LDH: Lactate Dehydrogenase
 γ-GTP: γ-Glutamyltranspeptidase
 CRP: C-reactive Protein

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions | Remarks |
|--|---------------|---|-----------------------------------|--|----------------|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 2 | Female 40s | Acute Bronchitis (myalgia, iron deficiency anaemia, acute gastroenteritis) | 500 mg 3 days | <p>White blood cell decreased, platelets decreased</p> <p>13 days before administration: The patient suffered from pyrexia, cough, snivel and abdominal pain, so she was treated with clarithromycin, tipepidine hibenzate, carbocisteine and general cold medicine.</p> <p>11 days before administration: Symptoms were improved, but treatment through medication was continued. For underlying anaemia and myalgia, administration of ferrous sulfate, ascorbic acid/calcium pantothenate and fursultiamine was initiated.</p> <p>On day 1 of administration: The patient visited hospital again due to exacerbation of symptoms (severe coughing, slight pyrexia of 38.0°C, and abdominal pain). Medication was changed (in antibiotics) to this drug, and the administration continued.</p> <p>On day 3 of administration (last day of administration): As pyrexia, sweaty and malaise did not improve, the patient received consultation at a general hospital. A blood test revealed white blood cell count was 920/mm³ and platelet count was 6.9 × 10⁴/mm³. The patient was hospitalized.</p> <p>4 days after completion: Recovery tendency was observed.</p> | Company report |
| Concomitant medications: ferrous sulfate, ascorbic acid/calcium pantothenate, fursultiamine, loxoprofen sodium, diclofenac sodium, d-chlorpheniramine maleate, cherry bark extract | | | | | |

Clinical Laboratory Values

| | 13 days before administration | On day 3 of administration (last day of administration) | 4 days after completion | 21 days after completion |
|---|-------------------------------|--|-------------------------|--------------------------|
| WBC (/mm ³) | 4380 | 920 | 2800 | 3450 |
| Platelet count (×10 ⁴ /mm ³) | 16.6 | 6.9 | 13.5 | 11.8 |
| Neutrophils (%) | 69.2 | -- | -- | 51.0 |

WBC: White Blood Cell

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions | Remarks |
|--|-------------|-----------------------------------|--------------------------------------|---|-------------------|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 3 | Male 30s | Acute tonsillitis (none) | 500 mg 2 days | <p>Rhabdomyolysis</p> <p>Drinking habit: Beer 500 mL/day</p> <p>1 day before administration: The patient had pyrexia starting in the evening.</p> <p>On day 1 of administration: During first medical examination, redness of the pharynx and tonsils was confirmed. There were no other pathological findings and the patient was diagnosed with acute tonsillitis. 500 mg of this drug, 180 mg of loxoprofen sodium, and 30 mg of serrapeptase were prescribed.</p> <p>On day 2 of administration (day of discontinuation): The patient noted bilateral abnormal fatigue in extremities (lack of power in extremities). Feelings of weakness confirmed in forearms (from elbow to palms) in upper extremities, and in thighs and leg region in lower extremities were confirmed.</p> <p>1 day after discontinuation: The patient noted abnormal fatigue in extremities since the previous day, and made another visit in the morning. Pyrexia (38°C to 39°C) from the first consultation persisted, and the patient had discontinued use of this drug based on his own judgment. Blood test was conducted, and Maoto extract granules were prescribed (the patient continued administration of loxoprofen sodium and serrapeptase as instructions to discontinue these drugs were not sufficiently conveyed). The patient went to work on this day. Since CK (CPK) had increased to 3016 IU/L in the night, the patient was instructed to make another visit the following day.</p> <p>2 days after discontinuation: In the morning, there was a trend towards an improvement in symptoms as compared to the previous day and the day before the previous day. Upon conducting another blood test, CK (CPK) was 9270 IU/L, LDH was 637 IU/L, blood myoglobin was 2190 ng/mL, and creatinine was 0.63 mg/dL.</p> <p>3 days after discontinuation: The patient was referred to another hospital. CK (CPK) was 7170 IU/L.</p> <p>4 days after discontinuation: CK (CPK) was 4560 IU/L. The patient received no particular treatment, and was followed up while resting at home.</p> <p>6 days after discontinuation: Subjective symptoms were mostly improved. CK (CPK) was 1962 IU/L.</p> <p>8 days after discontinuation: Urinalysis was conducted, and both protein and occult blood were negative. CK (CPK) was 804 IU/L, showing a gradual recovery trend.</p> <p>18 days after discontinuation: CK (CPK) recovered to 201 IU/L.</p> | Company report |
| Concomitant medications: loxoprofen sodium, serrapeptase | | | | | |

Clinical Laboratory Values

| | 1 day after discontinuation | 2 days after discontinuation | 3 days after discontinuation | 4 days after discontinuation | 6 days after discontinuation | 8 days after discontinuation | 18 days after discontinuation |
|-------------------------|-----------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|-------------------------------|
| CK (CPK) (IU/L) | 3016 | 9270 | 7170 | 4560 | 1962 | 804 | 201 |
| Blood myoglobin (ng/mL) | -- | 2190 | -- | -- | -- | -- | -- |
| Urine myoglobin (ng/mL) | -- | >3000 | | | | | |
| BUN (mg/dL) | -- | 18.4 | 17.0 | -- | -- | -- | -- |
| Creatinine (mg/dL) | -- | 0.63 | 0.67 | -- | -- | -- | -- |
| Na (mEq/L) | -- | 141 | 139 | -- | -- | -- | -- |
| K (mEq/L) | -- | 3.9 | 4.6 | -- | -- | -- | -- |
| Cl (mEq/L) | -- | 103 | 102 | -- | -- | -- | -- |
| AST (GOT) (IU/L) | -- | 257 | 270 | -- | 128 | -- | -- |
| ALT (GPT) (IU/L) | -- | 83 | 93 | -- | 97 | -- | -- |
| LDH (IU/L) | 347 | 637 | 547 | -- | 458 | -- | -- |
| Urinary occult blood | -- | (++) | | | | (-) | |
| Protein urine | -- | (+) | -- | -- | -- | (-) | -- |

CK: Creatine Kinase

BUN: Blood Urea Nitrogen

Na: Sodium

K: Potassium

Cl: Chloride

AST: Aspartate Aminotransferase

ALT: Alanine Aminotransferase

LDH: Lactate Dehydrogenase

Revision of PRECAUTIONS (No. 176)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 224), together with reference materials (excluding those presented in “1. Important Safety Information” of this Bulletin).

<Bronchodilators>

1 Clenbuterol Hydrochloride, Tulobuterol, Tulobuterol Hydrochloride, Procatamol Hydrochloride (oral dosage form), Formoterol Fumarate, Mabuterol Hydrochloride

[Brand Name]

Spiropent Granule, Spiropent Tablet (Teijin Pharma Limited) and others
 Hokunalin Tape 0.5 mg, 1 mg, and 2 mg (Abbott Japan Co., Ltd.)
 Berachin Tablets, Berachin Dry Syrup (Mitsubishi Pharma Corporation), Hokunalin Tablet 1 mg, Hokunalin Dry Syrup 0.1% Pediatric (Abbott Japan Co., Ltd.) and others
 Meptin Granules, Meptin-mini Tablets, Meptin Tablets, Meptin Syrup, Meptin Dry Syrup 0.005% (Otsuka Pharmaceutical Co., Ltd.) and others
 Atock Tablets 40 µg, Atock Dry Syrup (Astellas Pharma Inc.)
 Broncholin Tablets 25 and 50 (Kaken Pharmaceutical Co., Ltd.)

[Important Precautions]

The long-term management of bronchial asthma consists of the use of anti-inflammatory agents such as inhaled steroids. Concomitant use of this drug and inhaled steroids is only indicated, if inhaled steroids etc. cannot improve the symptoms or if it is judged from the severity of the patient's condition to be appropriate to use this drug concomitantly with inhaled steroids.
This drug is not a substitute for anti-inflammatory agents such as inhaled steroids etc. Therefore, the patient or his/her guardian, or other caregivers should be instructed not to reduce or discontinue inhaled steroids etc. and use this drug alone without the physician's instruction even if the patient experiences improvement of symptoms with the use of this drug.
For acute asthma attacks that may develop during the administration of this drug in the long-term management of bronchial asthma, the patient or his/her guardian, or other caregivers should be instructed to use other appropriate drugs such as short-acting inhaled β_2 -agonists.
If the dose of the drug used increases or the drug used becomes ineffective, the asthma control may be insufficient. In such a case, the patient or his/her guardian, or other caregivers should be instructed to visit a medical institution to receive treatment as soon as possible. As such condition may be life-threatening, the anti-inflammatory therapy should be intensified by taking measures such as dose increase of inhaled steroids etc.

2 <Miscellaneous metabolism agents>

2 Mycophenolate Mofetil

[Brand Name] Cellcept Capsules 250 (Chugai Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Pancytopenia, neutropenia (below 500/ μ L), agranulocytosis, leukopenia, thrombocytopenia, anaemia:** Since such symptoms may occur, conditions of the patient should be carefully monitored through periodic blood test, etc. If any abnormalities are observed, appropriate measures such as dose reduction, drug suspension, etc. should be taken.

<Reference Information> Company report

3 <Non-main therapeutic purpose agents-Miscellaneous>

3 Sodium Chloride/Potassium Chloride/Sodium Bicarbonate/Anhydrous Sodium Sulfate

[Brand Name] Niflec (Ajinomoto Pharma Co., Ltd.) and others

[Careful Administration] Patients who are prone to aspiration

[Important Precautions] Since pneumonia aspiration, dyspnoea, etc. may occur due to aspiration, caution should be exercised when administering this drug to patients who are prone to aspiration (elderly, patients with difficulty in swallowing, etc.).

[Adverse Reactions (clinically significant adverse reactions)] **Intestinal perforation, intestinal obstruction, incarcerated inguinal hernia:** Intestinal perforation, intestinal obstruction and incarcerated inguinal hernia may occur. The patients should be carefully monitored and if abnormalities are observed, administration should be discontinued, an abdominal examination and imaging tests (simple X-ray, ultrasound, CT scan etc.) should be conducted, and appropriate measures should be taken. Moreover, when administering this drug at home, patients should be instructed to refer to and follow the description in the "Important Precautions" section.

<Reference Information> Company report

3

List of products subject to Early Post-marketing Phase Vigilance

(As of June 1, 2006)

| Nonproprietary name ----- Brand name | Name of the marketing authorisation holder | Date of EPPV initiation |
|--|---|-------------------------|
| Moxifloxacin Hydrochloride ----- Avelox Tablets 400 mg | Bayer Yakuhin, Ltd. | December 9, 2005 |
| Finasteride ----- Propecia Tablets-0.2 mg and 1 mg | Banyu Pharmaceutical Co., Ltd. | December 14, 2005 |
| Miglitol ----- Seibule Tab. 25 mg, 50 mg, and 75 mg | Sanwa Kagaku Kenkyusho Co., Ltd. | January 11, 2006 |
| Potassium Clavulanate/Amoxicillin ----- Clavamox Dry Syrup for Pediatric | GlaxoSmithKline K.K. | January 17, 2006 |
| Paroxetine Hydrochloride Hydrate ----- Paxil Tablets 10 mg and 20 mg ^{*1} | GlaxoSmithKline K.K. | January 23, 2006 |
| Ciclosporin ----- Papilock Mini Ophthalmic Solution 0.1% | Santen Pharmaceutical Co., Ltd. | January 23, 2006 |
| Placental Gonadotrophin ----- Profasi Injection 5000 ^{*2} | Serono Japan Co., Ltd. | January 30, 2006 |
| Zanamivir Hydrate ----- Relenza ^{*3} | 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 ^{*4} | Toray Industries, Inc. | April 20, 2006 |
| Epoetin Beta (Genetical recombination) ----- Epogin Injection Ampoule 750, 1500, and 3000, Epogin Injection Syringe 750, 1500, and 3000 ^{*5} | Chugai Pharmaceutical Co., Ltd. | April 20, 2006 |
| Somatropin (Genetical recombination) ----- Humatrope C 6 mg and 12 mg ^{*6} | Eli Lilly Japan K.K. | April 20, 2006 |
| Zoledronic Acid Hydrate ----- Zometa Injection 4 mg ^{*7} | Novartis Pharma K.K. | April 20, 2006 |
| Micafungin Sodium ----- Funguard 50 mg and 75 mg for Infusion ^{*8} | Astellas Pharma Inc. | April 20, 2006 |
| Linezolid ----- Zyvox Tablets 600 mg, Zyvox Injection 600 mg ^{*9} | Pfizer Japan Inc. | April 20, 2006 |
| Clopidogrel Sulfate ----- Plavix Tablets 25 mg and 75 mg | Sanofi-Aventis K.K. | May 8, 2006 |
| Sildenafil ----- 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 |

| | | |
|--|-------------------------|--------------|
| Tosufloxacin Tosilate ----- Tosuflo Ophthalmic Solution 0.3% | Nidek 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 |

Note) Subject to additional indication etc.

*1: An additional indication for “obsessive-compulsive disorder”

*2: An additional indication for “induction of spermatogenesis in hypogonadotropic male hypogonadism”

*3: An additional administration for “pediatrics”

*4: 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 level)”

*5: An additional indication for “anaemia of prematurity”

*6: An additional indication for “adult growth hormone hyposecretion (for severe cases only)”

*7: Additional indications for “bone lesions due to multiple myeloma and solid tumor metastases to bone”

*8: An additional administration for “pediatrics”

*9: Additional indications 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”