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Pharmaceuticals and Medical Devices Agency

Revision of Precautions

Pioglitazone hydrochloride/metformin hydrochloride

June 18, 2019

Therapeutic category

Antidiabetic agents

Non-proprietary name

Pioglitazone hydrochloride/metformin hydrochloride

Safety measure

Precautions should be revised in the package insert.

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

Revision in line with the Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997 (Old instructions): Revised language is underlined.

Current	Revision
Warnings Serious lactic acidosis may occur. Cases of resultant patient mortality have been reported. This drug should not be administered to patients susceptible to lactic acidosis. Serious hypoglycaemia may also occur. The Dosage and Administration and Precautions sections of the package insert should be carefully considered.	Warnings Serious lactic acidosis may occur. Cases of resultant patient mortality have been reported. This drug should not be administered to patients susceptible to lactic acidosis. Careful administration is required in patients with renal or hepatic impairment or in elderly individuals through methods such as periodic assessment of renal or hepatic function. Particular caution should be exercised when considering the necessity of administration of this drug in the elderly 75 years or older.
Contraindications Patients under the following conditions: 1) History of lactic acidosis 2) Renal impairment (including mild impairment) 3) Dialysis patients (including peritoneal dialysis) 4) Patients with a severe disorder in the cardiovascular system and/or pulmonary function such as shock, cardiac failure, myocardial infarction and pulmonary embolism, or other conditions likely to be accompanied by hypoxemia 5) Patients with excessive alcohol consumption 6) Patients with dehydration or with gastrointestinal disorders such as diarrhoea and vomiting, which are signs of a state of dehydration. 7) The elderly Hepatic impairment	Contraindications The following patients: 1) Patients with a history of lactic acidosis 2) Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or dialysis patients (including peritoneal dialysis) 3) Patients with a severe disorder in the cardiovascular system and/or pulmonary function (such as shock, cardiac failure, myocardial infarction and pulmonary embolism), and patients with other conditions likely to be accompanied by hypoxemia 4) Patients with dehydration, or with signs of a state of dehydration (patients with gastrointestinal disorders such as diarrhoea and vomiting, patients with difficulty ingesting, etc.) 5) Patients with excessive alcohol consumption (deleted) Patients with severe hepatic impairment
(N/A)	Precautions concerning Dosage and Administration Since blood concentration of metformin may increase and the risk of lactic acidosis may increase in patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), attention should be paid to the following. This drug should be used in patients with eGFR

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
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<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td></td><td>≥30 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2 only if the expected therapeutic benefits outweigh the possible risks associated with treatment.
• Careful dose adjustment is required such as initiating treatment with this drug with metformin hydrochloride at a low dose and gradually increasing it while monitoring the effect. Appropriateness of this drug should be considered carefully compared with the alternative of co-administration of the individual pioglitazone and metformin preparations.
• Dosage of this drug should be determined considering the amount of pioglitazone and metformin hydrochloride contained in this drug as well as the approximate daily maximum doses of metformin hydrochloride alone in the table below.

(reference) Approximate maximum daily doses of metformin hydrochloride alone for patients with moderate renal impairment
<table><tr><th>Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m^2)</th><th>Approximate maximum daily dose</th></tr><tr><td>45≤ eGFR <60</td><td>1 500 mg</td></tr><tr><td>30≤ eGFR <45</td><td>750 mg</td></tr></table>*While the approved administration of metformin hydrochloride alone is administration of daily dosage in 2 or 3 divided doses, the approved administration of this drug (100 mg/250 mg or 100 mg/500 mg of anagliptin/metformin hydrochloride) is 1 tablet twice daily.

• Patients' conditions should be carefully monitored and necessity of administration of this drug and dose adjustment should be considered.</td></tr>
<tr><td>Careful Administration
The following patients or conditions:
(N/A)</td><td>Careful Administration
The following patients or conditions:
Mild to moderate renal impairment
Mild to moderate hepatic impairment
The elderly</td></tr>
</table>

Current	Revision
Important Precautions Serious lactic acidosis may rarely occur. The patient and their family should be fully instructed on the following because. 1) Excessive alcohol consumption should be avoided. 2) If there is a concern about a state of dehydration due to pyrexia, diarrhea, vomiting, poor meal ingestion, etc., patients should temporarily discontinue this drug and consult the physician. 3) Patients should seek immediate medical attention if they experience any initial symptoms of lactic acidosis. Dehydration may lead to lactic acidosis. When a symptom of dehydration is observed, this drug should be discontinued and appropriate measures be taken. When this drug is co-administered with a drug with diuretic action (diuretics, SGLT2 inhibitors, etc.), particularly careful attention should be paid for dehydration. The renal excretion of metformin decreases in patients with renal impairment, leading to increased blood concentration of metformin. Careful attention should be paid to the renal function and other condition of the patient, and the necessity of administration should be considered before and during treatment with this drug. eGFR, serum creatinine level, etc. should be referred to assess the renal function. Lactic acidosis may occur in patients who undergo a test using an iodinated contrast medium due to co-administration with this drug. This drug should be temporarily suspended before the test (except when the test needs to be urgently performed). This drug should not be resumed until 48 hours after an iodinated contrast medium is administered. Attention should be paid to the patient's condition when this drug is resumed.	Important Precautions Serious lactic acidosis may rarely occur. Known risk factors include renal impairment, hepatic impairment, conditions likely to be accompanied by hypoxemia, dehydration (including co-administration of drugs with diuretic effect), excessive alcohol consumption, infections, and the elderly. Especially, dehydration, excessive alcohol consumption, etc. may suddenly worsen patient's conditions. Attention should be paid to the following: 1) The patient should be assessed before and regularly during treatment with this drug for renal function (eGFR, etc.) and hepatic function. In addition, careful attention should be paid to the patient's condition and the necessity of administration and dosage adjustment should be considered. Patients requiring specifically careful follow-up including the elderly should be assessed more frequently. 2) When a symptom of dehydration is observed, this drug should be discontinued and appropriate measures be taken. When this drug is co-administered with a drug with diuretic action (diuretics, SGLT2 inhibitors, etc.), particularly careful attention should be paid to dehydration. 3) The patient and their family should be fully and properly instructed on the following at the start of and during the treatment with this drug. • Excessive alcohol consumption should be avoided. • When a patient suffers from physical deconditioning such as pyrexia, diarrhea, vomiting, poor meal ingestion, etc. (sick day), there is a concern about a state of dehydration. Therefore, the patient should discontinue this drug and consult with a physician. • When a symptom of lactic acidosis (gastrointestinal disorder, malaise, myalgia, hyperpnoea etc.) appears, the patient should consult with a physician immediately. 4) Lactic acidosis may occur in patients who undergo a test using an iodinated contrast medium due to co-administration with metformin. This drug should be temporarily suspended before the test (except when the test needs to be urgently performed). This drug should

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	not be resumed until 48 hours after an iodinated contrast medium is administered. Attention should be paid to the patient's condition when this drug is resumed.
Drug Interactions (N/A)	Drug Interactions Contraindications for Co-administration Alcohol (excessive consumption)
Geriatric Use In elderly individuals, renal or hepatic function is generally diminished. This drug should not be administered to elderly individuals who may be susceptible to lactic acidosis due to decreased renal excretion of metformin and reduced metabolic capacity as a result of diminished renal function.	Geriatric Use In elderly individuals, renal or hepatic function is often found diminished and dehydration tends to occur. These conditions make elderly individuals susceptible to lactic acidosis. Attention should be paid to the followings: 1) This drug should be administered carefully while closely monitoring patients through methods such as assessment of renal and hepatic function before and regularly during treatment with this drug. Patients requiring specifically careful follow-up should be assessed more frequently. 2) Patients should be closely monitored for their conditions such as renal function and dehydration, and discontinuation or dose reduction of this drug should be considered. Particularly careful consideration is required to decide whether administration of this drug is necessary or not in individuals 75 years or older because lactic acidosis is reported more often and prognosis tends to be poor in this age group. 3) Renal function may be actually diminished depending the age of patients even if their serum creatinine levels are within normal range. Patients should be carefully monitored for their conditions considering their eGRF etc.

N/A: Not Applicable, because the section is not included in the current package insert.

(reference) Sambol,N.C.,et al.:J.Clin.Pharmacol. 1995;35:1094