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Pharmaceuticals and Medical Devices Agency

Revision of Precautions

Metformin Hydrochloride

（preparations with a daily maximum dose of 2 250 mg）

June 18, 2019

Therapeutic category

Antidiabetic agents

Non-proprietary name

Metformin hydrochloride (preparations with a daily maximum dose of 2 250 mg)

Safety measure

Precautions should be revised in the package insert.

Pharmaceuticals and Medical Devices Agency

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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
Contraindications Patients under the following conditions: 1) History of lactic acidosis 2) Moderate or severe renal impairment 3) Dialysis patients (including peritoneal dialysis) 4) Severe hepatic impairment 5) 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 6) Patients with excessive alcohol consumption 7) Patients with dehydration or gastrointestinal disorders such as diarrhoea and vomiting, which are signs of a state of dehydration	Contraindications Patients under the following conditions: 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 severe hepatic impairment 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 patients with other conditions likely to be accompanied by hypoxemia 5) 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.) 6) Patients with excessive alcohol consumption
(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 ≥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. • Administration should be initiated at a low dose. • During administration, the patient should be monitored carefully through assessment of renal function (eGFR, etc.) more frequently, etc., and the necessity of administration and dose adjustment should be considered. • When the patient showed inadequate response to this drug, metformin hydrochloride can be administered up to the maximum daily dose based on the table below. The dose should be titrated up while closely monitoring the effect. The daily dose should be administered in 2 to 3 divided doses.

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<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td></td><td>Suggested maximum daily doses for patients with moderate renal impairment
<table><tr><th>Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m^2)</th><th>Suggested 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></td></tr>
<tr><td>Careful Administration
Patients under the following conditions:
Mild renal impairment</td><td>Careful Administration
Patients under the following conditions:
Mild to moderate renal impairment</td></tr>
<tr><td>Important Precautions
The patient and their family should be fully instructed on the following because this drug may rarely induces serious lactic acidosis.
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) If any initial symptoms of lactic acidosis are observed, patients should seek immediate medical attention.

Lactic acidosis may occur in patients who undergo a test using an iodinated contrast medium due to co-administration of 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.

Dehydration may lead to lactic acidosis. When a symptom of dehydration is observed, this drug should be discontinued and appropriate measures be taken. When co-administered with a drug with diuretic action (diuretics, SGLT2 inhibitors, etc.), particularly careful attention should be paid for dehydration.</td><td>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 the 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 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</td></tr>
</table>

Current	Revision
The renal excretion of this drug decreases in patients with renal impairment, leading to increased blood concentration. Attention should be paid to the following prior to and during treatment. 1) Careful attention should be paid to the renal function and other conditions of the patient, and the necessity of administration and dose adjustment should be considered. Refer to eGFR, serum creatinine level, etc. to assess the renal function. [The exclusion criteria of serum creatinine levels in clinical studies conducted in Japan: ≥1.3 mg/dL for adult men, ≥1.2 mg/dL for adult women, and >1.0 mg/dL for children (Refer to the Clinical Studies section).] 2) During treatment with this drug, renal function (eGFR, serum creatinine, etc.) should be monitored regularly, and more frequently when careful follow-up is required for elderly patients, etc. If deterioration of the renal function is observed, this drug should be discontinued or dosage should be reduced. Hepatic metabolism of lactic acid may decrease in patients with hepatic impairment. Patients should be regularly monitored for the liver function during treatment.	pyrexia, diarrhea, vomiting, poor meal ingestion, etc. (sick day), there is a concern about a state of dehydration. Therefore, the patient should temporarily 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 of 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.
Drug Interactions (N/A)	Drug Interactions Contraindications for Co-administration Alcohol (excessive consumption)

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