Published by
Ministry of Health, Labour and Welfare

Translated by
Pharmaceuticals and Medical Devices Agency

Revision of Precautions

Alogliptin benzoate /metformin hydrochloride

June 18, 2019

Therapeutic category

Antidiabetic agents

Non-proprietary name

Alogliptin benzoate/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
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
Precautions concerning Indications (N/A)	Precautions concerning Indications Careful administration is required with this drug in patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) through tapering alogliptin benzoate as well as metformin hydrochloride depending on the level of renal function. This drug should not be used and co-administration of individual preparations should be considered in patients with moderate renal impairment.
Important Precautions The patient and their family should be fully instructed on the following because metformin contained in 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.	Important Precautions Metformin contained in this drug may rarely induces serious lactic acidosis. 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 prior to and regularly during treatment with this drug for renal function (eGFR, etc.) and hepatic

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

Current	Revision
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. The renal excretion of metformin decreases in patients with renal impairment, leading to increased blood concentration of metformin. Attention should be paid to the following prior to and during treatment. 1) Careful attention should be paid to the renal function and other condition of the patient, and the necessity of administration should be considered. Refer to eGFR, serum creatinine level, etc. to assess the renal function. 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, discontinuation of this drug should be considered. Hepatic metabolism of lactic acid may decrease in patients with hepatic impairment. Patients should be regularly monitored for the liver function during treatment with this drug.	function. In addition, careful attention should be paid to the patient's condition and the necessity of administration 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 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.

Pharmaceuticals and Medical Devices Agency

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

Pharmaceuticals and Medical Devices Agency

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