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Pharmaceuticals and Medical Devices Agency

Revision of Precautions

Vildagliptin/metformin hydrochloride

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Therapeutic category

Antidiabetic agents

Non-proprietary name

Vildagliptin/metformin hydrochloride

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) 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.	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
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 vildagliptin as well as metformin hydrochloride depending on the degree of renal function. This drug should not be used and co-administration of individual drugs should be considered in patients with moderate renal impairment.
Important Precautions Serious lactic acidosis may rarely occur due to metformin, an active ingredient contained in this drug. The patient and their family should be fully instructed on the following. 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 suspend this drug and consult the physician. 3) Patients should seek immediate medical attention if they experience any initial symptoms of lactic acidosis. Hepatic function tests should be performed prior to, and in at least every	Important Precautions Serious lactic acidosis may rarely occur due to metformin, an active ingredient contained in this drug. 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 functions (eGFR, etc.) and hepatic functions. In addition, careful attention should be paid to the

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3 months for 1 year after the initiation of administration and then periodically thereafter. If any abnormalities are observed in hepatic test values such as ALT (GPT) or AST (GOT), appropriate measures should be taken such as discontinuing administration of this drug. If jaundice or other symptoms suggestive of hepatic impairment are observed, administration of this drug should be discontinued. A case has been reported associated with vildagliptin of elevated hepatic enzyme levels once recovered following discontinuation of administration but recurrent later. Administration of preparations containing vildagliptin including this drug should not be resumed after jaundice or other symptoms suggestive of hepatic impairment are recovered. 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 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 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 concentrations of metformin. Careful attention should be paid to the followings before and during administration: 1) Necessity of administration and dose adjustment should be considered before and during treatment with this drug. eGFR, serum creatinine level, etc. should be referred to assess the renal function. 2) Patients should be assessed before and regularly during treatment	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 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 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. Hepatic impairment (including hepatitis) may occur. Hepatic function tests should be performed before, and in at least every 3 months for 1 year after the initiation of administration and then periodically thereafter. If any abnormalities are observed in hepatic test values such as ALT (GPT) or AST (GOT), appropriate measures should be taken such as discontinuing administration of this drug. If jaundice or other symptoms suggestive of hepatic impairment are observed, administration of this drug should be discontinued. A case has been

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with this drug for renal functions (eGFR, serum creatinine, etc.). Patients requiring specifically careful follow-up including the elderly should be assessed more frequently. If deterioration in renal function is observed, measures should be taken such as discontinuing administration or dose reduction.	reported associated with vildagliptin of elevated hepatic enzyme levels that once recovered following discontinuation of administration but recurred later when administration was resumed. Administration of preparations containing vildagliptin including this drug should not be resumed after jaundice or other symptoms suggestive of hepatic impairment are recovered.
Drug Interactions (N/A)	Drug Interactions <u>Contraindications for Co-administration</u> <u>Alcohol (excessive consumption)</u>

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