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This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Revision of Precautions

Anagliptin/metformin hydrochloride

June 18, 2019

Therapeutic category

Antidiabetic agents

Non-proprietary name

Anagliptin/metformin hydrochloride

Safety measure

Precautions should be revised in the package insert.

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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
<p>Contraindications</p> <p>Patients under the following conditions:</p> <ol style="list-style-type: none"> 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. 	<p>Contraindications</p> <p>Patients under the following conditions:</p> <ol style="list-style-type: none"> 1) <u>Patients with</u> a history of lactic acidosis 2) <u>Patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) or dialysis patients (including peritoneal dialysis)</u> 3) <u>Patients with</u> 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 <u>patients with</u> other conditions likely to be accompanied by hypoxemia 5) <u>Patients with</u> dehydration, <u>or with</u> signs of a state of dehydration (patients with gastrointestinal disorders such as diarrhoea and vomiting, <u>patients with difficulty ingesting, etc.</u>) 6) Patients with excessive alcohol consumption
<p>(N/A)</p>	<p><u>Precautions concerning Dosage and Administration</u></p> <p><u>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 m² and <60 mL/min/1.73 m²), attention should be paid to the following: This drug should be used in patients with eGFR ≥30 mL/min/1.73 m² and <45 mL/min/1.73 m² only if the expected therapeutic benefits outweigh the possible risks associated with treatment.</u></p> <ul style="list-style-type: none"> • <u>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 preparations.</u> • <u>Dosage of this drug should be determined considering the amount of anagliptin and metformin hydrochloride contained in this drug as well as the approximate daily maximum doses of metformin hydrochloride alone suggested in the table below.</u>

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Current	Revision						
	<p data-bbox="1205 225 1962 284">(reference) <u>Approximate maximum daily doses of metformin hydrochloride alone for patients with moderate renal impairment</u></p> <table border="1" data-bbox="1133 309 1984 485"> <thead> <tr> <th data-bbox="1133 309 1617 373"><u>Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m²)</u></th> <th data-bbox="1621 309 1984 373"><u>Suggested maximum daily dose</u></th> </tr> </thead> <tbody> <tr> <td data-bbox="1133 376 1617 427">45 ≤ eGFR < 60</td> <td data-bbox="1621 376 1984 427">1 500 mg</td> </tr> <tr> <td data-bbox="1133 430 1617 481">30 ≤ eGFR < 45</td> <td data-bbox="1621 430 1984 481">750 mg</td> </tr> </tbody> </table> <p data-bbox="1160 520 1973 644">*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.</p> <ul data-bbox="1133 683 2002 742" style="list-style-type: none"> • <u>Patients' conditions should be carefully monitored and necessity of administration of this drug and dose adjustment should be considered.</u> 	<u>Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m²)</u>	<u>Suggested maximum daily dose</u>	45 ≤ eGFR < 60	1 500 mg	30 ≤ eGFR < 45	750 mg
<u>Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m²)</u>	<u>Suggested maximum daily dose</u>						
45 ≤ eGFR < 60	1 500 mg						
30 ≤ eGFR < 45	750 mg						
<p data-bbox="237 809 725 903">Careful Administration Patients under the following conditions: Mild renal impairment</p>	<p data-bbox="1133 809 1610 903">Careful Administration Patients under the following conditions: Mild <u>to moderate</u> renal impairment</p>						
<p data-bbox="237 906 1106 1318">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.</p> <ol data-bbox="264 1038 1106 1225" style="list-style-type: none"> 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. <p data-bbox="264 1264 1106 1318">Lactic acidosis may occur in patients who undergo a test using an iodinated contrast medium due to co-administration of this drug. This</p>	<p data-bbox="1133 906 2002 1318">Important Precautions Serious lactic acidosis may rarely occur due to metformin contained in this drug. <u>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:</u></p> <ol data-bbox="1160 1168 2002 1318" style="list-style-type: none"> 1) <u>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-</u> 						

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Current	Revision
<p>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.</p> <p>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.</p> <p>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.</p> <ol style="list-style-type: none"> 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 levels, etc. to assess the renal function. 2) During treatment with this drug, renal function (eGFR, serum creatinine levels, 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. <p>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.</p>	<p><u>up including the elderly should be assessed more frequently.</u></p> <ol style="list-style-type: none"> 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) <u>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.</u> <ul style="list-style-type: none"> • Excessive alcohol consumption should be avoided. • <u>When</u> a patient suffers from physical deconditioning such as pyrexia, diarrhea, vomiting, poor meal ingestion, etc. (<u>sick day</u>), there is a concern about a state of dehydration. <u>Therefore</u>, the patient should discontinue this drug and consult with a physician. • When a symptom of lactic acidosis (<u>gastrointestinal disorder, malaise, myalgia, hyperpnoea etc.</u>) 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.
<p>Drug Interactions (N/A)</p>	<p>Drug Interactions <u>Contraindications for Co-administration</u> <u>Alcohol (excessive consumption)</u></p>

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

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