



Metformin hydrochloride tablets (III)

【 Ingredients 】 The main ingredient of this product is metformin hydrochloride. Chemical name: 1,1-dimethylbiguanide hydrochloride. Molecular formula: $C_4H_{11}N_5 \cdot HCl$. Molecular weight: 165.63

【 Description 】 This product is a white coated tablet, which appears white after removing the coating.

[Indications] This product is used for adults with type 2 diabetes who are ineffective in simple diet control and physical exercise treatment. It can be treated with single drug, or combined with sulfonylurea drugs or insulin.

【 Usage and Dosage 】 It must be swallowed as a whole tablet and should not be crushed or chewed before use.

There is no fixed dose of this product for the treatment of hyperglycemia in type 2 diabetes. Individualize the dosage based on efficacy and tolerance, without exceeding the maximum recommended daily dose of 2500 mg.

This product is usually taken in a single dose with dinner. In order to reduce the occurrence of gastrointestinal complications and to use the minimum dose of medication to control the patient's blood sugar, it should be taken from a low dose and gradually increased.

During the start of treatment and adjustment of dosage (see recommended medication plan), measuring fasting blood glucose can be used to determine the treatment response of this product and determine the minimum effective dose for the patient. Afterwards, glycated hemoglobin should be measured every three months. Whether used alone or in combination with sulfonylurea drugs or insulin, the goal of treatment is to use the lowest effective dose to reduce fasting blood glucose and glycated hemoglobin levels to normal or near normal levels.

Recommended medication plan

Adults with normal renal function (eGFR \geq 90 mL/min/1.73m²)

The starting dose of this product is usually 500 mg once a day. It can be taken with a glass of water over dinner, or 1000 mg once a day according to clinical needs. Increase the weekly dose by 500 mg to a maximum dose of 2500 mg, once daily, taken with dinner.

A trial of converting patients treated with metformin hydrochloride tablets to metformin hydrochloride sustained-release tablets suggests that patients treated with metformin hydrochloride tablets can safely switch to metformin hydrochloride sustained-release tablets once a day at the same dose, up to 2500 mg once a day. After the transformation, blood sugar should be closely monitored and the dosage adjusted accordingly.

Transitioning from other hypoglycemic treatments to treatment:

Except for chloramphenicol, patients who switch from other oral hypoglycemic drugs to this product usually do not need a conversion period. Patients who take chloramphenicol should pay close attention to it during the first two weeks of switching to this product, as chloramphenicol has a long retention time in the body, which can easily lead to drug overdose and hypoglycemia.

Combined use with sulfonylurea drugs:

If patients who have not responded after taking the maximum recommended dose of this product for four weeks should consider gradually adding sulfonylurea oral hypoglycemic drugs while maintaining the maximum dose of treatment, unless the patient has already experienced failure to sulfonylurea drugs. Currently, there are only clinical and pharmacokinetic data on the interaction between metformin and glibenclamide (glibenclamide).

Combining this product with sulfonylurea drugs can achieve satisfactory blood sugar control by adjusting the dosage of both drugs. The risk of hypoglycemia caused by sulfonylurea drugs continues to exist and even increases when treated in combination with this product, and appropriate prevention should be taken. (See packaging instructions for the selected sulfonylurea drugs).

If the patient's blood sugar cannot be satisfactorily controlled after 1 to 3 months of treatment with the maximum dose of this product combined with the maximum dose of oral sulfonylurea drugs, it is necessary to consider changing the treatment method, including combining this product with insulin therapy or insulin therapy alone.

Temporary discontinuation of medication in patients undergoing iodide contrast imaging

Patients with eGFR between 45-60 mL/min/1.73m² should stop taking this product during or before

performing iodinated imaging. Patients with a history of liver injury, alcoholism, or heart failure should stop taking this product before performing arterial infusion iodinated imaging. Re evaluate eGFR 48 hours after the angiography is completed, and medication can be resumed after renal function is restored.

According to foreign literature reports, the most common adverse reactions during initial treatment include nausea, vomiting, diarrhea, abdominal pain, and loss of appetite, which most patients can usually alleviate on their own. The following adverse reactions may occur when taking metformin hydrochloride sustained-release tablets. The frequency of adverse reactions is defined as follows: very common ($\geq 10\%$); Common ($1\% \sim 10\%$, including 1%), occasional ($0.1\% \sim 1\%$, including 0.1%), rare ($0.01\% \sim 0.1\%$, including 0.01%), very rare (0.01%). In each frequency group, adverse reactions are arranged in descending order of severity. Metabolic and nutritional disorders: very rare: lactic acidosis (see [precautions]). Long term use of metformin may reduce the absorption of vitamin B12. If the patient develops megaloblastic anemia, this reason should be considered. Neurological abnormalities: Common: Taste disorders Gastrointestinal abnormalities: Very common: Gastrointestinal abnormalities such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite. These adverse reactions mostly occur at the beginning of treatment, and most patients can usually alleviate them on their own. Slowly increasing the dose can improve gastrointestinal tolerance. Abnormal liver and gallbladder function: Very rare: individual cases with abnormal liver function or hepatitis have been reported to return to normal after discontinuing the use of metformin. Skin and subcutaneous tissue abnormalities: very rare: skin reactions, such as erythema, itching, urticaria. Other possible adverse reactions include: bloating, fatigue, indigestion, abdominal discomfort and headache, abnormal bowel movements, constipation, bloating, hypoglycemia, muscle pain, dizziness, abnormal nails, rash, increased sweating, chest discomfort, chills, flu symptoms, hot flashes, palpitations, weight loss, accidental injuries, infections, rhinitis, etc. Adverse reactions reported after treatment with metformin on the market include bile stasis, liver cell and mixed liver cell damage.

【 Taboos 】 Severe renal failure (eGFR may affect acute conditions of renal function, such as dehydration, severe infection, shock; diseases that can cause tissue hypoxia (especially worsening of acute or chronic diseases), such as decompensated heart failure, respiratory failure, recent myocardial infarction, and shock; Severe infection and trauma, major surgical procedures, clinical symptoms such as hypotension and hypoxia; Known to be allergic to metformin hydrochloride and any components in

this product; Any acute metabolic acidosis, including lactic acidosis, diabetes ketoacidosis; Diabetes comatose prodromal stage; Liver dysfunction, acute alcoholism, and alcoholism; Individuals with uncorrected deficiencies in vitamin B12 and folate

【 Precautions 】 Warning of Lactic Acid Poisoning: Cases of Metformin related Lactic Acid Poisoning after marketing have led to death, hypothermia, hypotension, and refractory bradycardia. The onset of metformin related lactic acidosis is often concealed, accompanied by some non characteristic symptoms such as discomfort, muscle pain, difficulty breathing, drowsiness, and abdominal pain. The characteristics of metformin related lactic acidosis include elevated blood lactate levels (5 mmol/L), anionic interstitial acidosis (without ketonuria or ketosis), elevated lactate/pyruvate ratio, and plasma metformin concentration typically 5 μ G/mL. The risk factors for metformin related lactic acidosis include kidney injury, concomitant use of drugs (such as liver carbonate enzyme inhibitor topiramate), age 65 and above, use of contrast agents for radiation examinations, surgery and other procedures, hypoxia status (such as acute congestive heart failure), excessive alcohol consumption, and liver injury. Provided methods for reducing the risk of metformin related lactic acid poisoning in high-risk populations [see usage, dosage, contraindications, precautions]. If there is suspicion of metformin related lactic acidosis, the use of this product should be stopped immediately and general supportive treatment for hospitalization should be initiated. It is recommended to undergo hemodialysis immediately [see precautions]. General precautions for lactic acid poisoning: There have been reports of metformin related lactic acid poisoning, including death cases, since its launch. These patients have hidden onset and are only accompanied by non-specific symptoms such as discomfort, muscle pain, abdominal pain, respiratory distress, drowsiness, and in severe cases, may experience hypotension and refractory bradycardia. The characteristics of metformin related lactic acidosis include an increase in blood lactate levels (5 mmol/L), a decrease in blood pH (ketonuria or ketosis), anionic interstitial acidosis (without ketonuria or ketosis), an increase in lactate/pyruvate ratio, and a typical plasma concentration of metformin of 5 μ g/mL. Metformin can reduce the liver's intake of lactate, thereby increasing the level of lactate in the blood and increasing the risk of lactic acidosis, especially in high-risk patients. If there is suspicion of lactic acidosis related to metformin, general supportive treatment for hospitalization should be initiated immediately, and the use of this product should be stopped immediately. For patients who have taken this product and are diagnosed or highly suspected of lactic acidosis, it is recommended to immediately undergo hemodialysis to correct acidosis and

eliminate accumulated metformin (metformin hydrochloride can be dialyzed with a clearance rate of 170 mL/min when hemodynamic conditions are good). After such treatment, symptoms usually quickly alleviate and recover. Patients and their families should be educated on the symptoms of lactic acid poisoning. If symptoms occur, they should be instructed to immediately stop taking this product and seek medical attention. For every known and potential risk factor of metformin related lactic acid poisoning, the following methods are recommended to reduce risk and manage it: renal function impairment - post market metformin related lactic acid poisoning cases mainly occur in patients with obvious renal function impairment. Because metformin is mainly excreted through the kidneys, severe renal dysfunction increases the risk of metformin accumulation and related lactic acidosis.