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Metformin - A review

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ABSTRACT:

Metformin is used with a proper diet and exercise program and possibly with other medications to control high blood sugar. It is used in patients with type 2 diabetes. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen your risk of a heart attack or stroke. Metformin works by helping to restore your body's proper response to the insulin you naturally produce. It also decreases the amount of sugar that your liver makes and that your stomach/intestines absorb.

The dosage is based on your medical condition, response to treatment, and other medications you may be taking. Be sure to tell your doctor and pharmacist about all the products you use (including prescription drugs, non-prescription drugs, and herbal products). To reduce your risk of side effects (such as upset stomach), your doctor may direct you to start this medication at a low dose and gradually increase your dose. Follow your doctor's instructions carefully.

Take this medication regularly in order to get the most benefit from it. Remember to use it at the same times each day.

Introduction:

Metformin is an oral diabetes medicine that helps control blood sugar levels. Metformin is used together with diet and exercise to improve blood sugar control in adults with type 2 diabetes mellitus.

Metformin is sometimes used together with insulin or other medications, but it is not for treating type 1 diabetes.

Metformin is also used off-label to treat polycystic ovary syndrome (PCOS).

You should not use metformin if you are allergic to it, or if you have:

- severe kidney disease; or
- metabolic acidosis or diabetic ketoacidosis (call your doctor for treatment).

If you need to have surgery or any type of x-ray or CT scan using a dye that is injected into your veins, you may need to temporarily stop taking metformin. Be sure your caregivers know ahead of time that you are using this medication.

Tell your doctor if you have ever had:

- kidney disease (your kidney function may need to be checked before you take this medicine);
- high ketone levels in your blood or urine;
- heart disease, congestive heart failure;
- liver disease; or
- if you also use insulin, or other oral diabetes medications.

You may develop lacticacidosis**,** a dangerous build-up of lactic acid in your blood. This may be more likely if you have other medical conditions, a severe infection, chronic alcoholism, or if you are 65 or older. Ask your doctor about your risk.

Follow your doctor's instructions about using metformin if you are pregnant or you become pregnant. Controlling diabetes is very important during pregnancy, and having high blood sugar may cause complications in both the mother and the baby. Tell your doctor if you become pregnant while taking metformin.

Metformin may stimulate ovulation in a premenopausal woman and may increase the risk of unintended pregnancy. Talk to your doctor about your risk.

You should not breastfeed while using this medicine.

Metformin should not be given to a child younger than 10 years old. Some forms of metformin are not approved for use by anyone younger than 18 years old.

Take metformin exactly as prescribed by your doctor. Follow all directions on your prescription label and read all medication guides or instruction sheets. Your doctor may occasionally change your dose. Use the medicine exactly as directed.

Take metformin with a meal, unless your doctor tells you otherwise. Some forms of metformin are taken only once daily with the evening meal. Follow your doctor's instructions.

Do not crush, chew, or break an extended-release tablet. Swallow it whole.

Measure liquid medicine carefully. Shake the oral suspension before you measure a dose. Use the dosing syringe provided, or use a medicine dose-measuring device (not a kitchen spoon).

Some tablets are made with a shell that is not absorbed or melted in the body. Part of this shell may appear in your stool. This is normal and will not make the medicine less effective.

You may have low blood sugar **(**hypoglycemia**)** and feel very hungry, dizzy, irritable, confused, anxious, or shaky. To quickly treat hypoglycemia, eat or drink a fast-acting source of sugar (fruit juice, hard candy, crackers, raisins, or non-diet soda).

Your doctor may prescribe a glucagon injection kit in case you have severe hypoglycemia. Be sure your family or close friends know how to give you this injection in an emergency.

Blood sugar levels can be affected by stress, illness, surgery, exercise, alcohol use, or skipping meals. Ask your doctor before changing your dose or medication schedule.

Metformin is only part of a complete treatment program that may also include diet, exercise, weight control, regular blood sugar testing, and special medical care. Follow your doctor's instructions very closely.

Store at room temperature away from moisture, heat, and light.

Your doctor may have you take extra vitamin B12 while you are taking this medicine. Take only the amount of vitamin B12 that your doctor has prescribed.

If missed the dose take the medicine as soon as you can, but skip the missed dose if it is almost time for your next dose. Do not take two doses at one time.

An overdose can cause severe hypoglycemia or lactic acidosis.

Many drugs can interact with metformin, making it less effective or increasing your risk of lactic acidosis. This includes prescription and over-the-counter medicines, vitamins, and herbal products. Not all possible interactions are listed here. Tell your doctor about all your current medicines and any medicine you start or stop using.

Avoid drinking alcohol. It lowers blood sugar and may increase your risk of lactic acidosis.

metformin 1,000 mg tablet

Colour: white

Shape: oval

Imprint: G 12

This medicine is a white, oval, scored, film-coated, blackberry, tablet imprinted with "G 12".

metformin 850 mg tablet

Colour: white

Shape: round

Imprint: H 103

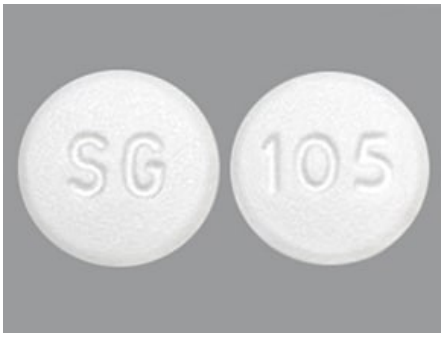
This medicine is a white, round, film-coated, tablet imprinted with "H 103".

metformin 500 mg tablet

Colour: white

Shape: round

Imprint: SG 105
This medicine is a white, round, film-coated, blackberry, tablet imprinted with "SG" and "105".



Uses of Metformin:

-As antidiabetic agent (type 2 diabetes):
Metformin is used with a proper diet and exercise program and possibly with other medications to control high blood sugar. It is used in patients with type 2 diabetes. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen your risk of a heart attack or stroke. Metformin works by helping to restore your body's proper response to the insulin you naturally produce. It also decreases the amount of sugar that your liver makes and that your stomach/intestines absorb.
Metformin lowers blood glucose and insulin levels in three ways:

1. It suppresses the liver's production of glucose.
2. It increases the sensitivity of your liver, muscle, fat and cells to the insulin your body makes.
3. It decreases the absorption of carbohydrates you consume.

-As anti- PCOS:
Although usually used to treat type 2 diabetes, metformin can also help relieve insulin resistance in PCOS. It works by improving insulin sensitivity, which decreases glucose production in your body and increases peripheral glucose uptake and utilization. This enables the cells of the body to absorb and use the glucose that's already available in your body.
Metformin has been studied in children as young as 8 years old who are diagnosed with PCOS or who have symptoms of the condition.[4] The drug can be safely administered at a dosage ranging from 500 milligrams (mg) to 2550 mg daily.[5]
-As antineoplastic agent:
In addition to its preventive action, the beneficial effect of metformin on improvement of overall survival outcomes or reduction in mortality was also observed in liver, pancreatic, colorectal, and breast cancer [Zhang et al., 2013; Morales and Morris, 2015)], suggesting that it can also serve as a potential anti-tumour agent [Jiralerspong et al., 2009].

Mechanism of action of metformin

As Anti-diabetic drug
The centre of metformin's mechanism of action is the alteration of the energy metabolism of the cell. Metformin exerts its prevailing, glucose-lowering effect by inhibiting hepatic gluconeogenesis and opposing the action of glucagon. The inhibition of mitochondrial complex I results in defective cAMP and protein kinase A signalling in response to glucagon. Stimulation of 5'-AMP-activated protein kinase, although dispensable for the glucose-lowering effect of metformin, confers insulin sensitivity, mainly by modulating lipid metabolism. Metformin might influence tumourigenesis, both indirectly, through the systemic reduction of insulin levels, and directly, via the induction of energetic stress; however, these effects require further investigation.

As Anti PCOS drug
Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease [R Dumitrescu, et al. 2015].

Pharmacokinetics
Absorption and Bioavailability

Given under fasting conditions the absolute bioavailability of a metformin hydrochloride 500 mg tablet is approximately 50% to 60%. Studies using single oral doses of metformin hydrochloride tablets of 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin.

Distribution

Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels do not exceed 5 mcg/mL, even at maximum doses.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following the oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is of approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metformin is not metabolized [Hardie DG, et al., 2007]. and is excreted unchanged in the urine, with a half-life of ~5 h [Grahm GG, et al. 2011]. The drug is widely distributed into the body tissues including the intestine, liver, and kidney by organic cation transporters [Grahm GG, et al. 2011]. There is a large interindividual variability in metformin pharmacokinetics as measured by differences in trough steady-state metformin plasma concentration ranging from 54 to 4133 ng/ml

Efficacy

The efficacy of metformin, both in monotherapy and in combination therapy, has been documented by a large number of studies, the most important of which will be briefly described in this section. Overall, metformin monotherapy has been estimated to lower HbA1c by approximately 1.5%. In combination, metformin can also significantly lower HbA1c, and the magnitude of the effect depends on the therapeutic combination, the follow-up of the study and the type of subjects recruited.

The glucose-lowering effect of metformin is clearly dose-dependent.36–38 In a 14-week, multicentre, double-blind study, Garber et al randomized 451 patients to placebo or metformin with doses of 500, 1000, 1500, 2000, or 2500 mg daily over 11 weeks.HbA1c dropped by -0.6% to -2.0% with increasing daily metformin dose (500 to 2000 mg), and differences between dosage groups were significant. Thisfavourable dose-response relationship has been confirmed.37,38 Fujioka et al randomized 742 patients to metformin extended-release 500 mg once daily, 1000 mg once daily, 1500 mg once daily, 2000 mg once daily, 1000 mg twice daily or placebo for 16 weeks, demonstrating a clear dose-response relationship at daily metformin doses between 500 mg and 1500 mg.In comparison with placebo, treatment differences amounted to -0.6% (500 mg once daily), -0.7% (1000 mg once daily), -1.0% (1500 mg once daily) and -1.0% (2000 mg once daily).38 It appears that 1500 mg and 2000 mg per day represent the optimal metformin dosages for most patients.

Metformin monotherapy has been assessed in a number of studies. A German trial randomized 96 patients to metformin 2 × 850 mg/day, acarbose 3 × 100 mg/day or placebo.39 It was shown that both drugs were equally active compared with placebo (p greater than0.05 for the comparisons with placebo): HbA1cdropped to 9.8% with placebo, 8.5% with acarbose, and 8.7% with metformin. Similarly, a study of 205 patients with recently diagnosed type 2 diabetes, who were randomized to either 30 mg pioglitazone or 850 mg metformin daily with titrations upward to 45 mg and 2550 mg, respectively, showed that both drugs were equally active. Specifically, HbA1c and fasting plasma glucose were comparable at the end of the study (pioglitazone: -1.3% reduction of HbA1c, p is greater than 0.0001 vs. baseline; metformin: -1.5% reduction of HbA1c, p is greater than 0.0001 vs. baseline; pioglitazone vs. metformin: p = 0.280).40 However, pioglitazone was significantly more effective than metformin in improving sensitivity (reduction of fasting serum insulin, p = 0.003; homeostasis model assessment, p = 0.002)[Saenz A, et.al., 2010].

The efficacy of metformin monotherapy has been evaluated in a very comprehensive Cochrane review.In this review, 29 trials with 5259 participants were included. Metformin was compared with sulphonylureas (13 trials), glitazones (3 trials), meglitindes (2 trials), α-glucosidase inhibitors (2 trials), placebo (12 trials), diet (3 trials) and insulin (2 trials). Metformin monotherapy was linked with a significant benefit in glycemic control, weight reduction, lipidemic profile and diastolic blood pressure. In terms of glycemic control, metformin was significantly superior to placebo diet and modestly better than sulphonylureas.Serum lipids and body weight were also improved with metformin than with sulphonylureas. The authors concluded that placebo, sulphonylureas, α-glucosidase inhibitors, glitazones, meglitinides, insulin and diet could not produce a more favourable effect on glycemic control, body weight, or serum lipids than metformin.

Not to be underestimated, metformin can be used in conjunction with various types of insulin. An international trial randomized 315 patients who were on metformin and/or a sulfonylurea with a stable dose of 0 to 2 daily insulin injections to receive insulin lispromix 50 (50% insulin lispro-protamine suspension and 50% lispro) three times daily plus metformin or bedtime insulin glargine plus metformin for 24 weeks.88 Both combinations managed to improve metabolic control. Metformin fared better with lispromix50 than glaring in terms of HbA1c, post-prandial hyperglycaemia and glycemic variability, whereas metformin plus glargine was superior in lowering fasting plasma glucose.88

Safety

Metformin is considered one of the safest oral hypoglycaemicagents. It reduces insulin resistance, but does not promote insulin secretion from β-cells, and thus it is not associated with increased risk of hypoglycemia. Minor untoward effects include nausea and diarrhea. They are usually mildand wane

over the first days of treatment. Nonetheless, they may be dose-limiting and reduce patient compliance.Such side effects may be minimized by using the sustained-release metformin formulation, which has been shown to be much better tolerated[Blonde ,et.al., 2009]. The major untoward effect is lactic acidosis. This condition still has a mortality up to 50%.However, it is now extremely rare, its incidence ranging between 0.01 and 0.15 per 1000 patient-years. More importantly, it virtually only occurs in patients with obvious contra-indications to metformin use. Contraindications are related to conditions predisposing to tissue hypoxia (congestive heart failure, chronic obstructive pulmonary disease, severe infection or gangrene), to liver disease, as well as to intrinsic or functional reduction of renal function (chronic renal failure, congestive heart failure, advanced age). This is explicable on the basis that metformin is cleared by the kidneys and that elevated serum lactic acid concentration may result either from severe tissue hypoxia or from reduced hepatic clearance owing to liver disease. Age itself is a much questioned contraindication, but most cases of lactic acidosis have been described in elderly patients, and several authors suggest avoidance of metformin in patients aged at least [DeFronzo RA., et.al, 2008].

Recently, the utility of the abovementioned contraindications has been debated. Even in patients with contra-indications, metformin associated lactic acidosis is very rare and occurs due to a superimposed medical condition. Mortality is then closely related with the degree of hypoxia, rather than serum metformin levels, casting doubt on the causal role of metformin[Scarpello JHB, et.al.,2008]. More impressively, several studies have shown that a considerable proportion of patients receiving 1 have formal contraindications to its use and yet never develop lactic acidosis. Nevertheless, these studies have been criticized for their retrospective observational design and for the variable interpretation of contraindications. In practice, lactic acidosis remains a potentially lethal condition, and, therefore, the clinician should assess patients carefully before prescribing metformin, in order to avoid those with serious contraindications.As long as contraindications and warnings are respected, metformin may be safely administered with almost no lactic acidosis.[CryerDR, et.al., 2005]

Cost-Effectiveness

Metformin has also proved cost-effective. The overall beneficial cost-effectiveness ratio has been estimated in various countries. In the UKPDS, cross-sectional surveys of non-inpatient healthcare use and quality of life revealed that the drug was cost-saving and that it increased life expectancy. A further analysis estimated the costs and effectiveness of intensive blood glucose control in overweight type 2 diabetes patients in China. Provided that one is willing to pay for quality-adjusted life year gained, intensive blood glucose control with metformin appears to be cost-effective. The average incremental costs of 11 years of intensive treatment with metformin amounted to 16400 US$ per quality-adjusted life year gained. The incremental cost-effectiveness ratio favoured metformin at 20 years (with 11700 US$) and 30 years (with 9600 US$)[Gray AM, et.al.,2008]. Using the UKPDS results, modelling techniques were applied to the Swiss health system, in order to estimate the cost-effectiveness of the management type 2 diabetic patients by conventional vs. intensive control with metformin. Total cost (including both diabetes therapy and management of new-onset complications) and survival were determined over an 11-year period. Mean total cost per patient was 10877 Swiss Francs for conventional vs. 9950 Swiss Francs for intensive control with metformin. IN addition, intensive control with metformin prolonged survival by a mean of 0.43 life-years per patient.A further analysis evaluated the cost-effectiveness of metformin vs. lifestyle changes for patients with impaired glucose tolerance in Australia, France, Germany, Switzerland, and the United Kingdom. Both interventions were cost-effective in all countries, except for United Kingdom, where cost was slightly increased with either intervention[Xie X, et.al., 2008].

Drug interaction

Pharmacokinetic drug interactions of Metformin

Metformin is a cation at physiological pH, as it is a strong base. Hence, the absorption, distribution and excretion of Metformin depend on the transporters such as Organic Cation Transporters (OCTs), Multidrug and Toxin Extruders (MATEs) and Plasma membrane Monoamine Transporter (PMAT).The oral absorption and hepatic uptake of Metformin are mediated possibly by Organic cation transporters (OCTs) (OCT1 and OCT3) and renal excretion of Metformin is largely mediated by Metformin transporters such as Multidrug and Toxin Extruders (MATEs) MATE1 and MATE2-k and Organic cation transporter 2 (OCT2).Metformin is not metabolized and excreted unchanged in urine and the patients with moderate and severe chronic renal impairment (CRI) should not be administered with metformin. As Metformin is not metabolized, it is not expected to be involved in many drug–drug interactions (DDIs).

Metformin use is associated to Lactic Acidosis probably due to the accumulation of lactate through the inhibition of hepatic glucose production from lactate molecules.The drugs inhibiting the Metformin transporters (MATEs and OCTs) could decrease the elimination of Metformin and increase it's plasma concentrations leading to elevated risk of Metformin Associated Lactic Acidosis (MALA).Metformin administration should be stopped and urgent medical attention given to the patients developing first signs of MALA such as severe vomiting and diarrhea.

Interactions with Iodinated Contrast Materials (ICM)

Iodinated Contrast Materials (ICMs) used widely and successfully during many procedures including angiography, urography, etc. Administration of iodinated contrast media (CM) would result in Contrast-induced nephropathy (CIN) Hence, the risk of toxic accumulation of Metformin and subsequent Lactic Acidosis may be higher in patients taking Metformin who undergo procedures using Iodinated contrast material (ICM). The risk is further increased in patients with renal impairment and it is recommended to stop Metformin while using ICM in patients with renal impairment.

Interactions with acid suppressing agents

H_2 receptor blockers

Cimetidine

Cimetidine is a potent inhibitor of Multidrug and toxin extruder 1 (MATE1) of proximal tubular epithelial cells and it is a broad-spectrum inhibitor of transporters including Organic Cation Transporter 2 (OCT 2). Concomitant use of Metformin and Cimetidine decrease the excretion of Metformin, resulting in increased exposure of Metformin and elevated risk of Metformin Associated Lactic Acidosis (MALA).It is recommended to reduce the dose of Metformin when Cimetidine is co-prescribed.

Ranitidine

Ranitidine is a potential inhibitor of Multidrug and Toxin Extruder 1 (MATE1) and hence the renal clearance of Metformin decreased.

Famotidine

Famotidine may be suitable H2 blocker in patients taking Metformin, as it is a selective inhibitor of MATE1 and increasing the therapeutic efficacy of Metformin by significantly increasing the estimated bioavailability of Metformin. In addition, Famotidine enhances the renal clearance of Metformin compared to Cimetidine or Ranitidine which decrease it's elimination.

Proton pump inhibitors

Proton pump inhibitors may inhibit Multidrug and toxin extruder (MATE) and OCT2 transporters and increase plasma metformin exposure. It is recommended to monitor the concomitant use of Proton pump inhibitors with Metformin.

The risk of Vitamin B12 deficiency was found to be elevated by the combination of Proton pump inhibitors or H_2 receptor blockers and Metformin. The malabsorption of vitamin B12 promoted by additive effects of Proton pump inhibitors or H_2 receptor blockers and Metformin. Concomitant use of these drugs should be monitored for the consequences such as peripheral neuropathy and megaloblastic anaemia. It is recommended for Vitamin B12 replacement in patients taking Metformin and PPIs/ H_2 receptor blockers to prevent cobalamin deficiency.

Interaction with Antimicrobials

Trimethoprim

Trimethoprim inhibits Metformin elimination moderately through the inhibition of OCTs and MATEs, but the co-administration of both the drugs should be carried out carefully in patients with renal dysfunction or patients taking higher doses of Metformin.

Cephalexin

Cephalexin is a zwitterionic substrate of MATE1and it reduces the elimination of Metformin resulting in accumulation.

Rifampin

Hepatic uptake of Metformin might be elevated by the administration of Rifampin due to increased expression of OCT1.

Dolutegravir

Dolutegravir is used as the first-line antiretroviral agent in the treatment of HIV infection and it is an inhibitor of both OCT2 and MATE1 transporters within the renal tubules. Concomitant use of Dolutegravir and Metformin may result in increased adverse effects of Metformin such as hypoglycemia and GI intolerance caused by increased plasma concentrations of Metformin occurred due to the inhibition of OCT2 and MATE1 transporters. Prescribers may adjust the Metformin dose to prevent intolerable ADRs while prescribing Dolutegravir and Metformin concurrently.

Pyrimethamine

Pyrimethamine is an antiparasitic drug and is used to treat toxoplasmosis and cystoisosporiasis. Pyrimethamine is an inhibitor of both OCT2 and MATE transporters. Co-administration of Pyrimethamine with Metformin results in elevated plasma concentrations due to decreased renal clearance of Metformin induced by the inhibition of OCT2 and MATE transporters by Pyrimethamine.

Interaction with Ranolazine

Ranolazine is approved to treat chronic angina. Ranolazine blocks sodium channel of pancreatic α cells and decreases electrical activity to inhibit glucagon release.The plasma concentrations of Metformin may be elevated by the co-administration of Ranolazine which may decrease the Metformin elimination through the inhibition of OCT2 transporter. This interaction is dose dependent and it is recommended that the daily dose of Metformin should not exceed 1700 mg in patients taking Ranolazine 1000 mg two times daily.

Interaction with Anticancer Drugs

Vandetanib

Vandetanib is used in the treatment of medullary thyroid cancer. Vandetanib is a potent inhibitor of MATE1 and MATE2K transportersand its co-administration with Metformin may result in increased plasma concentrations of Metformin due to decreased elimination as it is the substrate of MATE1 and MATE2K transporters. The patients receiving the combination of Vandetanib and Metformin should be monitored carefully for Metformin toxicity.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors such as Imatinib, Nilotinib, Gefitinib, and Erlotinib may reduce the elimination of Metformin by inhibiting OCTs and MATEs transporters, at clinically relevant concentrations.

Interaction with Beta adrenergic blockers

Atenolol

The plasma concentration of Metformin may be elevated due to reduced elimination induced by Atenolol as it reduces the renal blood flow and inhibits OCT2 competitively.

Metoprolol

The plasma concentration of Metformin can be decreased by Metoprolol by increasing the hepatic uptake of Metformin through the induction of OCT1, increasing the renal uptake of Metformin by reducing the expression of MATE1 and increasing the uptake of Metformin in thigh muscle through the induction of OCT3

Drug – food interaction:

Metformin should be taken with meals, and excessive alcohol intake (either short-term binge drinking or frequent consumption) should be avoided during treatment. Taking metformin with alcohol may increase the risk of a rare but serious and potentially life-threatening condition known as lactic acidosis, which is a build-up of lactic acid in the blood that can occasionally occur during treatment with metformin-containing products. Lactic acidosis is more likely to occur if you have kidney or liver disease, acute or unstable congestive heart failure, or dehydration. You should seek

immediate medical attention if you develop potential signs and symptoms of lactic acidosis such as fatigue, weakness, muscle pain, increasing drowsiness, abdominal pain or discomfort, slow or irregular heartbeat, breathing difficulty, chills, and other unusual symptoms. Alcohol may also affect blood glucose levels in patients with diabetes. Both hypoglycemia (low blood sugar) and hyperglycaemia (high blood sugar) may occur, depending on how much and how often you drink. You should avoid using alcohol if your diabetes is not well controlled or if you have high triglycerides, neuropathy (nerve damage), or pancreatitis. Moderate alcohol consumption generally does not affect blood glucose levels if your diabetes is under control. However, you should limit your alcohol intake due to the risk of lactic acidosis with metformin. Avoid drinking alcohol on an empty stomach or following exercise, as it may increase the risk of hypoglycemia. Talk to your doctor or pharmacist if you have any questions or concerns about metformin.

Metformin side effects

Commonly reported side effects of metformin include: lactic acidosis, diarrhea, nausea, nausea and vomiting, vomiting, and flatulence.
Other side effects include: asthenia, and decreased vitamin b12 serum concentrate. See below for a comprehensive list of adverse effects.
Get emergency medical help if you have signs of an allergic reaction to metformin**:** hives; difficult breathing; swelling of your face, lips, tongue, or throat.
Some people using this medicine develop lactic acidosis, which can be fatal. Get emergency medical help if you have even mild symptoms such as:

- unusual muscle pain;
- feeling cold;
- trouble breathing;
- feeling dizzy, light-headed, tired, or very weak;
- stomach pain, vomiting; or
- slow or irregular heart rate.

Common metformin side effects may include:

- low blood sugar;
- nausea, upset stomach; or
- diarrhea.

Side effects requiring immediate medical attention
Along with its needed effects, metformin may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.
Check with your doctor immediately if any of the following side effects occur while taking metformin:
More common

- Abdominal or stomach discomfort
- cough or hoarseness
- decreased appetite
- diarrhea
- fast or shallow breathing
- fever or chills
- general feeling of discomfort
- lower back or side pain
- muscle pain or cramping
- painful or difficult urination
- sleepiness

Less common

- Anxiety
- blurred vision
- chest discomfort
- cold sweats
- coma
- confusion
- cool, pale skin
- depression
- difficult or laboured breathing
- dizziness
- fast, irregular, pounding, or racing heartbeat or pulse
- feeling of warmth
- headache
- increased hunger
- increased sweating
- nausea
- nervousness

- nightmares
- redness of the face, neck, arms, and occasionally, upper chest
- seizures
- shakiness
- slurred speech
- tightness in the chest
- unusual tiredness or weakness
- Rare
- Behavior change similar to being drunk
- difficulty with concentrating
- drowsiness
- lack or loss of strength
- restless sleep
- unusual sleepiness

Side effects not requiring immediate medical attention

Some side effects of metformin may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects.

Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:

More common

- Acid or sour stomach
- belching
- bloated
- excess air or gas in the stomach or intestines
- full feeling
- heartburn
- indigestion
- loss of appetite
- metallic taste in the mouth
- passing of gas
- stomach-ache
- stomach upset or pain
- vomiting
- weight loss

Less common

- Abnormal stools
- bad, unusual, or unpleasant (after) taste
- change in taste
- difficulty with moving
- discoloration of the fingernails or toenails
- flu-like symptoms
- joint pain
- rash
- sneezing
- stuffy or runny nose
- swollen joints

General

Gastrointestinal events such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite have been frequently reported during therapy initiation and resolve spontaneously in most cases.

Adverse events in the paediatric population appear to be similar in nature and severity to that published in adults.

Metabolic

Common (1% to 10%): Hypoglycemia

Very rare (less than 0.01%): Lactic acidosis[Ref]

Gastrointestinal

Very common (10% or more): Diarrhea (53.2%), nausea/vomiting (25.5%), flatulence (12.1%)

Common (1% to 10%): Indigestion, abdominal discomfort, abnormal stools, dyspepsia, loss of appetite

Hematologic

Very rare (less than 0.01%): Subnormal vitamin B12 levels

Common (1% to 10%): Asthenia, chills, flu syndrome, accidental injury

Hepatic

Very rare (less than 0.01%): Liver function test abnormalities, hepatitis

Cardiovascular
Common (1% to 10%): Chest discomfort, flushing, palpitation
Dermatologic
Common (1% to 10%): Rash, nail disorder, increased sweating
Very rare (less than 0.01%): Erythema, pruritus, urticarial
Endocrine
Frequency not reported: Reduction in thyrotropin (TSH) levels
Immunologic
Very common (10% or more): Infection (20.5%)
Musculoskeletal
Common (1% to 10%): Myalgia
Nervous system
Common (1% to 10%): Light-headedness, taste disturbances
Psychiatric
Common (1% to 10%): Headache
Respiratory
Common (1% to 10%): Rhinitis

Metformin HCL - Uses, Side Effects, and More

COMMON BRAND(S): GLUCOPHAGE
GENERIC NAME(S):

Precaution
See also warning section.
taking this medication, tell your doctor or pharmacist if you are allergic to metformin; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.
Before using this medication, tell your doctor or pharmacist your medical history, especially of: severe breathing problems (such as obstructive lung disease, severe asthma), blood problems (such as anaemia, vitamin B12 deficiency), kidney disease, liver disease.
Before having surgery or any X-ray/scanning procedure using iodinated contrast, tell your doctor or dentist about all the products you use (including prescription drugs, non-prescription drugs, and herbal products). You may need to stop this medication for a short time for the surgery/procedure. Ask your doctor or dentist for instructions before your surgery/procedure.
You may experience blurred vision, dizziness, or drowsiness due to extremely low or high blood sugar. Do not drive, use machinery, or do any activity that requires alertness or clear vision until you are sure you can perform such activities safely.
Limit alcohol while using this medication because it can increase your risk of lactic acidosis and developing low blood sugar.
High fever, "water pills" (diuretics such as hydrochlorothiazide), too much sweating, diarrhea, or vomiting may cause dehydration and increase your risk of lactic acidosis. Stop taking this medication and tell your doctor right away if you have prolonged diarrhea or vomiting. Be sure to drink enough fluids to prevent dehydration unless your doctor directs you otherwise.
It may be harder to control your blood sugar when your body is stressed (such as due to fever, infection, injury, or surgery). Consult your doctor because increased stress may require a change in your treatment plan, medications, or blood sugar testing.
Older adults may be at greater risk for side effects such as low blood sugar or lactic acidosis.
During pregnancy, this medication should be used only when clearly needed. Discuss the risks and benefits with your doctor. Your doctor may direct you to use insulin instead of this product during your pregnancy. Follow your doctor's instructions carefully.
Metformin can cause changes in the menstrual cycle (promote ovulation) and increase the risk of becoming pregnant. Consult your doctor or pharmacist about the use of reliable birth control while using this medication.
Metformin passes into breast milk in small amounts. Consult your doctor before breast-feeding.

Contraindications
The following conditions are contraindicated with this drug. Check with your physician if you have any of the following:
Conditions:
- an infection
- low blood sugar
- pituitary hormone deficiency
- decreased function of the adrenal gland
- inadequate vitamin B12
- excess body acid
- dehydration
- alcoholism
- alcohol intoxication

- a heart attack
- sudden and serious symptoms of heart failure called acute decompensated heart failure
- liver problems
- fever
- a condition where the body is unable to maintain adequate blood flow called shock
- excessive vomiting
- excessive diarrhea
- serious lack of oxygen in the blood
- weakened patient
- sepsis
- chronic kidney disease stage 3B (moderate)
- chronic kidney disease stage 4 (severe)
- chronic kidney disease stage 5 (failure)
- kidney disease with likely reduction in kidney function
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Warnings

You should not use metformin if you have severe kidney disease, metabolic acidosis, or diabetic ketoacidosis (call your doctor for treatment).

If you need to have any type of x-ray or CT scan using a dye that is injected into your veins, you may need to temporarily stop taking metformin.

Though extremely rare, you may develop lactic acidosis**,** a dangerous build-up of lactic acid in your blood. Call your doctor or get emergency medical help if you have unusual muscle pain, trouble breathing, stomach pain, dizziness, feeling cold, or feeling very weak or tired.

Conclusions:

Metformin has a long history in the management of type 2 diabetes and is now the most widely prescribed oral hypoglycaemic agent. Its main modes of action encompass anorexiogenesis, reduction of intestinal carbohydrate absorption, inhibition of hepatic gluconeogenesis, as well as increased glucose uptake by peripheral tissues. Metformin has been established as the drug of choice for the first-line treatment of type 2 diabetes, and its administration has been strongly suggested at diagnosis of this metabolic disorder, alongside diet and exercise. It may also be successfully combined with all other oral hypoglycaemic agents and insulin. Of greater importance, this agent has been consistently.

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