

**METFORMIN**

Glucophage®

# METFORMIN

**GLUCOPHAGE (metformin hydrochloride) Tablets** is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus.

## **Metformin can cause:**

- + Metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias.
- + Decrease to subnormal levels of previously normal serum vitamin B12 levels
- + Cholestatic
- + Hepatocellular
- + Mixed hepatocellular liver injury
- + Diarrhea
- + Nausea/Vomiting
- + Abdominal pain
- + Constipation
- + Distention abdomen

- + Palpitation
- + Changes in your blood sugar
- + Unpleasant metallic taste in mouth
- + Sweating increased
- + Taste disorder
- + Chest discomfort
- + Chills
- + Flu syndrome
- + Flushing
- + Dyspnea
- + Nail disorder
- + Rash
- + Hypoglycemia
- + Myalgia
- + Lightheaded
- + Dyspepsia/heartburn
- + Flatulence
- + Dizziness
- + Headache
- + Upper respiratory infection
- + Taste disturbance
- + Asthenia
- + Abnormal stools

**SOURCES FROM FDA + MERCK SANTÉ**

# METFORMIN



<https://medlineplus.gov/druginfo/meds/a696005.html>

## **Other brand names:**

+ Fortamet®

+ Glumetza®

+ Riomet®

+ Trijardy® (as a combination product containing Empagliflozin, Linagliptin, Metformin)

+ Metformin may be present in combination products as well. For the full list, go to the above NIH link.

**This medication may cause changes in your blood sugar. You should know the symptoms of low and high blood sugar and what to do if you have these symptoms.**

Metformin may cause other side effects. Call your doctor if you have any unusual problems while taking this medication.

You should always wear a diabetic identification bracelet to be sure you get proper treatment in an emergency.

# LACTIC ACIDOSIS

## **WARNING: LACTIC ACIDOSIS**

**Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL (see PRECAUTIONS).**

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

# PREGNANCY

GLUCOPHAGE or GLUCOPHAGE XR are not recommended for use in pregnancy.

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, GLUCOPHAGE and GLUCOPHAGE XR should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with GLUCOPHAGE or GLUCOPHAGE XR.



<https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/gestational/management-treatment>

## Managing & Treating Gestational Diabetes

Your health care team will help you make a healthy eating plan with food choices that are good for you and your baby. The plan will help you know which foods to eat, how much to eat, and when to eat. Food choices, amounts, and timing are all important in keeping your blood glucose levels in your target range.

Physical activity can help you reach your target blood glucose levels. If your [blood pressure](#) or [cholesterol](#) levels are too high, being physically active can help you reach healthy levels.

# MANAGING DIABETES

High blood sugar can be lowered by diet and exercise, by a number of medicines taken by mouth, and by insulin shots. Before you take GLUCOPHAGE or GLUCOPHAGE XR, try to control your diabetes by exercise and weight loss. While you take your diabetes medicine, continue to exercise and follow the diet advised for your diabetes. No matter what your recommended diabetes management plan is, studies have shown that maintaining good blood sugar control can prevent or delay complications of diabetes, such as blindness.



<https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/type-2-diabetes>

Managing your blood glucose, [blood pressure](#), and [cholesterol](#), and quitting smoking if you smoke, are important ways to [manage your type 2 diabetes](#). Lifestyle changes that include planning healthy meals, limiting calories if you are overweight, and being physically active are also part of managing your diabetes.

**Lose weight if you are overweight, and keep it off.** You may be able to prevent or delay diabetes by losing 5 to 7 percent of your current weight.<sup>1</sup> For instance, if you weigh 200 pounds, your goal would be to lose about 10 to 14 pounds.

**Move more.** Get at least 30 minutes of physical activity, such as walking, at least 5 days a week. If you have not been active, talk with your health care professional about which activities are best. Start slowly and build up to your goal.

# OFF-LABEL USE: PCOS



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9440853/>

Polycystic ovarian syndrome (PCOS) is an endocrine disorder. This condition is characterized by chronic anovulation and ovarian dysfunction, unlike other ovulation disorders when the ovaries are non-functional or abnormal. Currently, most therapy is centred on the patient's primary complaint. Treatment focuses on reducing hyperandrogenism symptoms, restoring menstrual regularity, and achieving conception.



<https://pubmed.ncbi.nlm.nih.gov/35156149/>

**Results:** Metformin increases success rates and decreases complication rates when used as an adjunctive medication for ovulation induction during low complexity assisted reproduction treatments and during ovarian stimulation for in vitro fertilization in women with PCOS. Evidence about the effect of metformin on fetal and obstetric complication rates is conflicting. Metformin is associated with high incidence of gastrointestinal symptoms; however, serious adverse effects are rare and there is no evidence of teratogenicity.

**Conclusion:** For women with PCOS, metformin is a good adjunctive medication for ovulation induction/stimulation for high and low complexity assisted reproduction therapies. The adverse effects are mostly mild, and there is no risk of teratogenicity, but the risk of long-term complications for the offspring is not yet defined. High heterogeneity of the studies limits extrapolation of findings, and further research is needed to determine which women will benefit most from the medication.

# METFORMIN IN REPRODUCTIVE BIOLOGY



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6262031/>

In rodents, prenatal exposure to metformin modifies the hepatic fetal imprinting resulting in changes in the expression of several genes involved in the metabolism of cholesterol, lipids, fatty acids and steroids. Moreover, it decreases the expression of insulin-sensitive glucose transporter, GLUT4, in epididymal adipose tissue suggesting long-term effects, such as glucose intolerance in the testis (99). In a follow-up study of metformin in a gestational diabetes trial showed that prenatal exposure had a change in the pattern of fat distribution in children at 2 years-old (same body fat mass but more subcutaneous fat (102). Taken together these studies point to a putative epigenetic effect of metformin which could be exerted during perinatal periods.

After half a century, metformin has established itself as a first defense against insulin-dependent morbidities and undoubtedly has become a useful drug for improving fertility outcomes in both male and female patients. Metformin can modify testis and ovary function directly through AMPK-dependent and independent mechanisms. Its effects include improved sperm function and fertilization rates, oocyte quality and embryo development and reduction in miscarriage rates. The general consensus in the literature is that metformin is considered safe to use during pregnancy in regards to perinatal outcomes. However, adverse effects of metformin in the germ cell populations of offsprings exposed *in utero* and those on subsequent generations are less clear. While our understanding of the effects of metformin is continually progressing, further research is needed to have a more complete understanding of metformin's impact on fertility.



# VITAMIN B12 DEFICIENCY



<https://www.ncbi.nlm.nih.gov/books/NBK518983/>

Prolonged use of metformin has been associated with decreased vitamin B12 levels; therefore, healthcare professionals should carefully monitor patients, especially those with anemia or peripheral neuropathy. In some cases, supplementation of vitamin B12 may be necessary.<sup>[2]</sup>



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561829/>

Vitamin B-12 deficiency (<148 pmol/L) is associated with adverse maternal and neonatal outcomes, including developmental anomalies, spontaneous abortions, preeclampsia, and low birth weight (<2500 g). The importance of adequate vitamin B-12 status periconceptionally and during pregnancy cannot be overemphasized, given its fundamental role in neural myelination, brain development, and growth. Infants born to vitamin B-12-deficient women may be at increased risk of neural tube closure defects, and maternal vitamin B-12 insufficiency (<200 pmol/L) can impair infant growth, psychomotor function, and brain development, which may be irreversible.

**Other infant outcomes.** Additional infant outcomes assessed in relation to maternal vitamin B-12 status included excessive crying and insulin resistance.

Several studies have also noted an association between low maternal vitamin B-12 status during early pregnancy and insulin resistance in children later in life

# INGREDIENTS

GLUCOPHAGE tablets contain 500 mg, 850 mg, or 1000 mg of metformin hydrochloride. Each tablet contains the inactive ingredients povidone and magnesium stearate. In addition, the coating for the 500 mg and 850 mg tablets contains hypromellose and the coating for the 1000 mg tablet contains hypromellose and polyethylene glycol.

GLUCOPHAGE XR contains 500 mg or 750 mg of metformin hydrochloride as the active ingredient.

GLUCOPHAGE XR 500 mg tablets contain the inactive ingredients sodium carboxymethyl cellulose, hypromellose, microcrystalline cellulose, and magnesium stearate.

GLUCOPHAGE XR 750 mg tablets contain the inactive ingredients sodium carboxymethyl cellulose, hypromellose, and magnesium stearate.



<https://www.ncbi.nlm.nih.gov/books/NBK557652/>

Polyethylene glycol (PEG) is a product with industrial and pharmaceutical uses.

Polyethylene glycol is a medication that is used in the management and treatment of constipation. It is in the laxative class of drugs.

Common side effects of oral administration of PEG include flatulence, nausea, stomach cramps, diarrhea, swollen abdomen, and rectal hemorrhage.[13][14]