

## PRODUCT INFORMATION

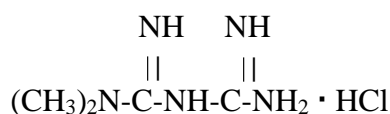
### METFORMIN SANDOZ® 1000mg FILM COATED TABLETS

#### NAME OF THE MEDICINE

Generic name: Metformin hydrochloride.

Chemical name: *N,N*-dimethylbiguanide hydrochloride.

Chemical structure:



CAS number: [1115-70-4]

MW: 165.63

#### DESCRIPTION

Metformin hydrochloride is a white, odourless or almost odourless, hygroscopic, crystalline powder. It is freely soluble in water, slightly soluble in alcohol, and practically insoluble in acetone and methylene chloride.

Metformin Sandoz 1000 mg tablets contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, copovidone, colloidal anhydrous silica, magnesium stearate, lactose, hypromellose, titanium dioxide and macrogol 4000.

#### PHARMACOLOGY

Metformin causes an increased peripheral uptake of glucose by increasing the biological efficiency of available exogenous or endogenous insulin. The mode of action of metformin may be linked to an increase of insulin sensitivity. It does not stimulate insulin release but does require the presence of insulin to exert its antihyperglycaemic effect. Possible mechanisms of action include inhibition of gluconeogenesis in the liver, delay in glucose absorption from the gastrointestinal tract and an increase in peripheral uptake of glucose.

Metformin has an antiketogenic activity which is comparable, though somewhat inferior, to insulin itself. metformin lowers both basal and postprandial blood glucose in diabetic patients but does not cause hypoglycaemia in either diabetics or normal individuals.

#### Pharmacokinetics

In a bioavailability study, the mean C<sub>max</sub> and AUC values after a single oral dose of metformin 1000 mg (fasting state) was  $2.16 \pm 0.58 \mu\text{g/mL}$  and  $12.36 \pm 4.01 \mu\text{g/mL}$  respectively.

#### *Absorption*

After oral administration, metformin hydrochloride is absorbed along the entire gastrointestinal mucosa. Studies using single oral doses of metformin tablets indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an increase in elimination. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are nonlinear.

Maximum plasma concentrations are attained 2.5 to 3.5 hours after oral dosing.

At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations are reached in 24 to 48 hours and are generally less than 1 microgram/mL. During controlled clinical trials, maximum metformin plasma levels did not generally exceed 5 microgram/mL, even at maximum doses.

#### *Distribution*

Metformin is not bound to plasma proteins.

#### *Metabolism*

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism.

#### *Excretion*

In patients with decreased renal function (based on measured creatinine clearance), the plasma half-life of metformin is prolonged and renal clearance is decreased in proportion to the decrease in creatinine clearance, e.g. if creatinine clearance is 10 to 30 mL/minute, renal clearance is reduced to 20% of normal.

## **CLINICAL TRIALS**

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed the following:

- a significant reduction of the absolute risk of any diabetes related complication in the metformin group (29.8 events/ 1,000 patient years) versus diet alone (43.3 events/ 1,000 patient years),  $p = 0.0023$ , and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/ 1,000 patient years),  $p = 0.0034$ ;
- a significant reduction of the absolute risk of diabetes related mortality: metformin 7.5 events/ 1,000 patient years, diet alone 12.7 events/ 1,000 patient years,  $p = 0.017$ ;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1,000 patient years versus diet alone 20.6 events/ 1,000 patient years ( $p = 0.011$ ), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/ 1,000 patient years ( $p = 0.021$ );
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1,000 patient years, diet alone 18 events/ 1,000 patient years ( $p = 0.01$ ).

For metformin used as second line therapy, in combination with a sulfonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

## INDICATIONS

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

Metformin may be used as initial treatment or in sulfonylurea failures either alone or in combination with a sulfonylurea and other oral agents or as adjuvant therapy in insulin dependent diabetes.

## CONTRAINDICATIONS

- Juvenile diabetes mellitus that is uncomplicated and well-regulated on insulin.
- Diabetes mellitus regulated by diet alone.
- During or immediately following surgery where insulin is essential.
- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/minute).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see PRECAUTIONS).
- Acute or chronic disease which may cause tissue hypoxia such as cardiac failure, recent myocardial infarction, respiratory failure, pulmonary embolism, shock, acute significant blood loss, sepsis, gangrene, pancreatitis.
- Elective major surgery (see PRECAUTIONS)
- Severe hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Lactation.

## PRECAUTIONS

### Lactic acidosis

Lactic acidosis is a rare but serious (high mortality in the absence of prompt treatment), metabolic complication which can occur due to metformin accumulation during treatment with metformin. When it occurs, it is fatal in approximately 50% of cases. Lactic acidosis is a medical emergency and must be treated in hospital immediately. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, often in the setting of multiple concomitant medical/ surgical problems and multiple concomitant medications.

The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Special caution should be taken in the elderly due to the decrease of renal function with age.

The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1,000 patient years, with approximately 0.015 fatal cases per 1,000 patient years). The onset is often subtle and accompanied by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and nonspecific abdominal distress. Lactic acidosis may also occur in association with a number of pathophysiological conditions, including diabetes mellitus, and when there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is characterised by acidosis (decreased blood pH), elevated lactate levels with increased lactate/pyruvate ratio and electrolyte disturbances with an increased anion gap.

#### Diagnosis

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see **OVERDOSAGE - Treatment**).

#### Heart failure

Type 2 diabetic patients with heart failure are at an increased risk of hypoperfusion and possible renal insufficiency. Renal insufficiency is a risk factor for systemic accumulation of metformin and consequently lactic acidosis. Careful monitoring of renal function is recommended when metformin is used in patients with cardiac failure. The major risk of cardiac insufficiency is hypoxia.

#### Renal function

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function,
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.

When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 microgram/mL are generally found (see PHARMACOKINETICS). Underlying renal disease, or a deterioration in renal function, result in reduced clearance of metformin and drug accumulation and are therefore major risk factors in lactic acidosis. The risk of lactic acidosis may therefore be significantly decreased by regular monitoring of renal function in patients taking metformin and those patients on concomitant diuretics. The use of the minimum effective dose of metformin is recommended. In addition, metformin therapy should be temporarily stopped in the presence of any condition associated with hypoxaemia or dehydration, in patients suffering from serious infections or trauma (particularly if gastrointestinal disturbances are noted or acidosis is suspected) and in those undergoing surgery.

### Surgery

Metformin must be discontinued 48 hours before elective major surgery. Therapy may be restarted no earlier than 48 hours following surgery and only after normal renal function has been re-evaluated and found to be normal.

### Other precautions

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g sulphonylureas or meglitinides).

Patients receiving continuous metformin therapy: It is recommended that serum vitamin B12 levels be measured prior to initiation treatment with metformin, after 6 months treatment and thereafter annually because of reports of decreased vitamin B12 absorption associated with metformin administration.

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should therefore be warned against excessive alcohol intake, acute or chronic, while taking metformin. Periodic assessment of renal, hepatic and cardiovascular function is recommended during prolonged periods of treatment with metformin.

### Administration of iodinated contrast agent

Radiological studies involving the use of intravascular iodinated contrast materials (for example intravenous urogram, intravenous cholangiography, angiography, any computed tomography scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, metformin must be discontinued either 48 hours before the test when renal function is known to be impaired or from the time of the test when renal function is known to be normal. Metformin may not be reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see **Precautions - Interactions with other medicines**).

### Use in the elderly

The risk of lactic acidosis, in association with metformin, is increased in elderly patients on long-term therapy due to the physiological alteration of the renal function and the possible accumulation of metformin. Metformin may be used in the elderly if Contraindications and Precautions are respected, the dosage is frequently reviewed and renal function monitored.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired.

### Carcinogenicity

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 and 1,500 mg/kg/day, respectively. These doses are both approximately two to three times the recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in

either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

#### Genotoxicity

No evidence of a mutagenic potential of metformin was found in the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or in vivo micronuclei formation test (mouse bone marrow).

#### Impairment of Fertility

Fertility of male or female rats was unaffected by metformin administration at doses up to 600 mg/kg/day, or approximately twice the maximum recommended daily dose on a body surface area basis.

#### Use in pregnancy (Category C)

*Australian Category C Definition:* Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Oral hypoglycaemics may enter the fetal circulation and cause neonatal hypoglycaemia. It is important to achieve strict normoglycaemia during pregnancy. Oral antihyperglycaemic agents should be replaced by insulin.

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks. The safety of metformin in pregnant women has not been established.

Information available suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. There is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

#### Use in lactation

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in breastfeeding mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

#### Paediatric Use

Metformin is not recommended for use in children, except those with insulin resistant diabetes who are being treated in hospital.

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. No effect of metformin on growth and puberty has been detected during controlled clinical

studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended.

## INTERACTIONS WITH OTHER MEDICINES

**Cimetidine.** Reduced clearance of metformin has been reported during cimetidine therapy, so a dose reduction should be considered.

**Anticoagulants.** Metformin increases the elimination rate of vitamin K antagonists. Consequently, the prothrombin time should be closely monitored in patients in whom metformin and vitamin K antagonists are being coadministered. Cessation of metformin in patients receiving vitamin K antagonists can cause marked increases in the prothrombin time.

**Nifedipine.** A single dose, metformin/ nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of metformin and nifedipine increased plasma metformin C<sub>max</sub> and AUC by 20 and 9%, respectively, and increased the amount of metformin excreted in the urine. T<sub>max</sub> and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on the pharmacokinetics of nifedipine.

**Sulfonylureas and meglitinides.** During concomitant therapy with other antidiabetic agents, such as sulfonylureas or meglitinides, blood glucose should be monitored because combined therapy may cause hypoglycaemia.

**Beta-blockers.** Coadministration of metformin and beta-blockers may result in a potentiation of the antihyperglycaemic action. In addition, some of the premonitory signs of hypoglycaemia, in particular tachycardia, may be masked. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

### **ACE inhibitors.**

ACE-inhibitors may decrease the blood glucose levels. Therefore, dose adjustment of metformin hydrochloride may be necessary when such medicinal products are added or discontinued.

**Calcium channel blockers.** Calcium channel blockers may affect glucose control in diabetic patients; regular monitoring of glycaemic control is recommended.

**Alcohol.** The risk of lactic acidosis increases with acute alcohol intoxication, particularly in cases of fasting or malnutrition and hepatic insufficiency. Alcohol may make the signs of hypoglycaemia less clear and delayed hypoglycaemia may occur. The CNS depressant effects of alcohol plus hypoglycaemia can make driving or the operation of dangerous machinery much more hazardous. Avoid consumption of alcohol and alcohol-containing medications.

**Thiazide diuretics.** Thiazide therapy may impair glucose tolerance. Dosage adjustment of metformin may be required.

**Thyroid products.** Thyroid products tend to produce hyperglycaemia and may lead to loss of control.

**Combinations requiring precautions for use:**

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, chlorpromazine at high dosages of 100 mg per day and diuretics:

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon discontinuation.

**Diuretics especially loop diuretics**, may increase the risk of lactic acidosis due to their potential to decrease renal function.

**Iodinated contrast media.**

Metformin must be discontinued either 48 hours before the test when renal function is known to be impaired, or from the time of the test when renal function is known to be normal (see Precautions - Administration of iodinated contrast materials).

**Other:** Phenothiazines, oestrogens, oral contraceptives, phenytoin, nicotinic acid sympathomimetics and isoniazid tend to produce hyperglycaemia and patients receiving concomitant administration of any of these drugs with metformin hydrochloride should be closely observed to maintain glycaemic control.

Effects on Laboratory Tests.

No information is available.

Effects on ability to drive or operate machinery

Patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (sulphonylureas, glinides, insulin).

## ADVERSE EFFECTS

**Gastrointestinal disorders.** Very common. Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite) are the most frequent reactions to metformin (> 1/10), especially during the initial treatment period. These symptoms are generally transient and resolve spontaneously during continued treatment.

Gastrointestinal side effects can possibly be avoided if metformin is taken with meals and if the dose is increased slowly. Occasionally, a temporary dose reduction can be considered. Occurrence of gastrointestinal symptoms, once a patient is stabilised on any dose of metformin, could be due to lactic acidosis or other serious disease.

**Metabolism and nutrition disorders.** Very rare. Lactic acidosis (see PRECAUTIONS) is a very rare (< 1/10,000) but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin.



The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's doctor must be aware of the possible importance of such symptoms and the patient should be instructed to notify the doctor immediately if they occur. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in hospital. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted.

A decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long-term with metformin, and appears to be generally without clinical significance (< 1/10,000). Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia. Therefore, serum B12 levels should be appropriately monitored or periodic parenteral B12 supplementation considered. (see Precautions).

**Nervous System Disorders.** Common: Taste disturbance (3%) is common.

**Skin and subcutaneous tissue disorders.** Very rare. Skin reactions such as mild erythema, pruritus and urticaria have been reported in some hypersensitive individuals, but the incidence is very rare (< 1/10,000).

**Hepatobiliary Disorders.** Very rare: Isolated reports of Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, have been reported.

## DOSAGE AND ADMINISTRATION

**Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment; other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g/day.**

It is important that the tablets are taken in divided doses with meals.

Initially 500 mg should be taken once or twice a day and, if necessary, increased over a few weeks up to 1 g three times per day. The dose should be titrated with gradual dose increments until the desired effect is obtained. 500 mg three times a day is often sufficient to obtain diabetic control. If necessary, the dose can be increased to 1 g three times daily, which is the maximum recommended daily dose. Control may be attained within a few days but occasionally requires up to two weeks. Once control has been obtained, the dosage should be reviewed and reduced to the lowest maintenance level consistent with good diabetic control.

Metformin dosage should be frequently reviewed in patients stabilised on metformin, especially if they develop an illness, as they may tolerate the drug less well, particularly if the illness is

accompanied by a decrease in renal function. If necessary, metformin should be ceased for a few days during an illness and then restarted at low dosage, as for initial therapy.

The action of metformin is progressive and no final assessment of the patient's real response should be made before the 21st day of treatment; blood sugar estimations are recommended during the initial 15 days of stabilisation. Metformin will not produce a hypoglycaemic state when used alone; however, due to its action in increasing insulin effectiveness, care must be taken when metformin is initially administered with parenteral doses of insulin.

**Elderly.** The initial and maintenance dosing of metformin should be conservative in elderly patients, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin.

**Debilitated or malnourished patients.** In debilitated or malnourished patients, the dosing should be conservative and based on a careful assessment of renal function.

## OVERDOSAGE

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

### Symptoms

Hypoglycaemia has not been seen with ingestion of up to 85 g of metformin alone, although lactic acidosis has occurred in such circumstances. The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

### Treatment

Lactic acidosis should be feared in diabetic metformin treated patients with overdose. Lactic acidosis is diagnosed and monitored by measurement of serum electrolytes, arterial pH and pCO<sub>2</sub> and arterial lactate plasma level.

The aim of treatment is to manage any underlying disorder and in some cases this will be sufficient to enable the body's homeostatic mechanism to correct the acid/ base imbalance. The advantages of more active treatment of the acidosis must be balanced against the risks, including overalkalinisation with sodium bicarbonate. Because metformin hydrochloride is dialysable (with a clearance of up to 170 mL/minute under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

## PRESENTATION AND STORAGE CONDITIONS

Metformin Sandoz 1000 mg tablets: white, oblong, biconvex film-coated tablets scored on both sides. Embossed M 1000 on one side. 90's

Store below 25°C.

**NAME AND ADDRESS OF THE SPONSOR**

Sandoz Pty Ltd  
ABN 60 075 449 553  
54 Waterloo Road  
Macquarie Park, NSW 2113  
Australia  
Tel: 1800 634 500

**POISONS SCHEDULE**

S4 – Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 02/02/2010**

**DATE OF MOST RECENT AMENDMENT: 13/04/2016**