

New Zealand Data Sheet

1. PRODUCT NAME

Indoco Metformin 500mg Film Coated Tablet

Indoco Metformin 850mg Film Coated Tablet

Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Indoco Metformin 500mg Film Coated Tablet contains 500mg metformin hydrochloride.

Indoco Metformin 850mg Film Coated Tablet contains 850mg metformin hydrochloride.
For a full list of excipients, see *Section 6.1*.

3. PHARMACEUTICAL FORM

Indoco Metformin 500mg Film Coated Tablet: white to off white, circular, biconvex film coated tablet with beveled edges.

Indoco Metformin 850mg Film Coated Tablet: white to off white, circular, biconvex film coated tablet with beveled edges.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

To control hyperglycemia in metformin responsive, stable, mild, non-ketosis prone, maturity onset type of diabetes (Type II) which cannot be controlled by proper dietary management, exercise and weight reduction or when insulin therapy is not appropriate. It may be used alone or in combination with sulphonyl urea therapy.

- Metformin can be of value for the treatment of obese diabetics.
- It may also be used as adjuvant therapy in insulin-dependent diabetics especially if they are overweight.

4.2. Dose and method of administration

This product may not be interchangeable with other products containing this ingredient in the New Zealand market.

Life threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and doses of metformin above 2 g per day (see Section 4.4).

Dose

Adults

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

Monotherapy and combination with other oral antidiabetic agents in adults with normal renal function

Initially 500 mg should be taken once or twice a day and, if necessary, increased over a few weeks up to a maximum of 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. 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.

The maximum dose of 3g daily should only be used in patients with good renal function (creatinine clearance greater than 120 mL/min).

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 stabilization. Metformin will not produce a hypoglycemic state when used alone; however, it increases insulin effectiveness.

Combination with insulin or sulphonylureas in adults

Metformin therapy with a sulphonyl urea or insulin should be monitored by blood-sugar readings because combined therapy may cause hypoglycemia. If it is decided to stabilize diabetic patients with metformin and insulin therapy, it is recommended that this is carried out in hospital until the correct ratio of the two medicines is determined because of the possibility of hypoglycemia.

Special populations

Elderly population

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.

Renal impairment

The risk of lactic acidosis is increased in patients with renal impairment. Metformin is contraindicated in patients with renal failure (creatinine clearance <15 mL/min) (see Section 4.3).

Metformin may be used in patients with **stable** renal impairment (but *see Section 4.4*). Where possible the dose should be titrated with gradual dose increments.

The maximum daily dose for patients with creatinine clearance between 15-30 mL/min is 500mg.

The maximum daily dose for patients with creatinine clearance between 30-60 mL/min is 1000 mg.

The maximum daily dose for patients with creatinine clearance between 60-120 mL/min is 2000 mg.

It is recommended that metformin concentrations are checked after steady state has been reached (after 48 hours) to ensure metformin concentrations remain below 5 microgram/mL (5 mg/L).

Renal function should be closely monitored (every 3-6 months).

If the creatinine clearance drops below 15mL/min metformin must be discontinued.

Debilitated or malnourished patients

The dosing should be conservative and based on a careful assessment of renal function.

Paediatric population

Metformin is not recommended for use in children (*see Section 4.4 for more information*).

Method of Administration

For oral administration

4.3. Contraindications

Metformin is contraindicated in the following conditions:

- 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 and other biguanides, or to any of the excipients listed in *Section 6.1*
- Diabetic ketoacidosis, diabetic precoma
- Renal failure (creatinine clearance <15 mL/minute), patients with unstable renal function
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (*see Section 4.4*)

- Acute conditions which may cause tissue hypoxia such as cardiac failure, recent myocardial infarction, respiratory failure, pulmonary embolism, acute significant blood loss, sepsis, gangrene, pancreatitis
- Severe hepatic insufficiency, acute alcohol intoxication, alcoholism
- History of lactic acidosis
- Lactation (*see Section 4.6 for more information*).

4.4. Special warnings and precautions for use

Lactic acidosis

Lactic acidosis is a rare but serious metabolic complication which can occur due to metformin accumulation during treatment. When it occurs, it is fatal in more than 25% 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 acute conditions causing a significant decrease in renal function or tissue hypoxia (*see Section 4.3*). Hepatic dysfunction is also a risk as lactate clearance is reduced (*see Section 4.3*). Patients with long-term stable conditions should be carefully assessed prior to treatment for risk factors for lactic acidosis such as: poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and conditions associated with hypoxia (*see Section 4.3*).

Particular caution should be paid in situations where renal function may become impaired such as dehydration, when starting therapy with a diuretic or when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In these situations metformin should be temporarily discontinued.

When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 microgram/mL (5mg/L) are generally found (*see Section 5.2*).

Diagnosis

The risk of lactic acidosis must be considered in the event of non-specific signs such as malaise, myalgia, muscle cramps, respiratory distress, increasing somnolence and non-specific abdominal distress.

Patients should be instructed to notify these signs to their physician immediately.

As lactic acidosis progresses there may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. This can be followed by acidotic dyspnea and coma. Lactic acidosis is characterized by acidosis (decreased blood pH), elevated lactate levels above 5 mmol/L with increased lactate/pyruvate ratio and

electrolyte disturbances with an increased anion gap. If there is any suspicion of metabolic/lactic acidosis metformin should be discontinued and the patient hospitalized immediately. Prompt haemodialysis is recommended to correct the acidosis and remove accumulated metformin (*see Section 4.9*).

Renal Impairment

Underlying renal disease, or deterioration in renal function, result in reduced clearance of metformin and drug accumulation and are therefore major risk factors in lactic acidosis (*see Section 4.2*). 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 twice a year in patients with impaired renal function and elderly patients

Decreased renal function in elderly subjects is frequent and asymptomatic.

Metformin therapy should be temporarily stopped in the presence of any condition associated with hypoxemia 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.

Prompt haemodialysis is recommended to correct the acidosis and remove accumulated metformin (*see Section 4.9*).

Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory (NSAID).

Metformin is contraindicated in patients with creatinine clearance below 15 mL/min.

Hepatic Impairment

Impaired hepatic function may significantly limit the ability to clear lactate. Metformin should be avoided in patients with severe hepatic insufficiency (*see Section 4.3*) and used with caution in patients with milder disease.

Heart Failure

Type 2 diabetic patients with heart failure are at an increased risk of hypo-perfusion and possible renal insufficiency. Careful monitoring of renal function is recommended when metformin is used in patients with cardiac failure.

Administration of iodinated contrast media

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 should be stopped at least 48 hours prior to, during and for 2 days after the radiological studies. For an emergency procedure, metformin should be stopped on admission. Metformin should be reinstated only after renal function has been re-evaluated and found to be normal.

Surgery

Metformin must be discontinued 48 hours before elective surgery under general, spinal or peridural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

Alcohol

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.

Other precautions

Periodic assessment of renal, hepatic and cardiovascular function is recommended during prolonged periods of treatment with metformin.

Patients receiving continuous metformin therapy should have an annual estimation of vitamin B12 levels because of reports of decreased vitamin B12 absorption.

Special populations

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 when the issues raised under *Section 4.3 and Section 4.4* have been taken into consideration, the dosage is frequently reviewed and the renal function is closely monitored.

Use in children

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

4.5. Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

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 co-administered. 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 co-administration of metformin and nifedipine increased plasma metformin C_{max} and AUC by 20 and 9%, respectively, and increased the amount of metformin excreted in the urine. T_{max} and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on the pharmacokinetics of nifedipine.

Pharmacodynamic interactions

Sulfonylureas and repaglinide

During concomitant therapy with sulfonylureas and repaglinide, blood glucose should be monitored because combined therapy may cause hypoglycemia.

Beta-blockers

Co-administration of metformin and beta-blockers may result in a potentiation of the hypoglycemic action. In addition, some of the premonitory signs of hypoglycemia, in particular tachycardia, may be masked. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

ACE inhibitors

Co-administration of metformin and ACE inhibitors may result in a potentiation of the hypoglycemic action. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent

Calcium channel blockers

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

Thyroid products

Thyroid products tend to produce hyperglycemia and may therefore lead to loss of control.

Corticosteroids

Corticosteroids tend to produce hyperglycemia and may lead to loss of control.

Alcohol

Alcohol decreases blood glucose concentration by inhibiting hepatic glucose output, thus increasing the risk of hypoglycemia and can also mask its warning symptoms. The CNS depressant effects of alcohol plus hypoglycemia can make driving or the operation of dangerous machinery much more hazardous. Excessive consumption of alcohol while on metformin may result in elevation of blood lactate.

Thiazide diuretics

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

Iodinated contrast media

Metformin should be temporarily withheld in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (*see Section 4.4*).

Laboratory tests

No information is available.

4.6. Fertility, pregnancy and lactation

Pregnancy

Uncontrolled diabetes in pregnancy is associated with an increased risk of congenital abnormalities and perinatal mortality. The foetus is significantly exposed to metformin taken by the mother; in some cases exposure was as high as maternal exposure. Therefore metformin should only be used in pregnancy if the potential benefits to the mother and foetus outweigh the risks of harm, taking into consideration the benefits and risks of other treatments such as insulin.

Effects on the mother and child

The current data on use of metformin in the first trimester are insufficient to determine whether there are any risks to the foetus. Metformin was not teratogenic in rats and rabbits at doses of up to 600 mg/kg/day. However, *In vitro* tests investigating genotoxicity and embryo toxicity have suggested that metformin may have weak toxic effects.

Data are available from a meta-analysis of randomized controlled trials comparing metformin with insulin in gestational diabetes. Metformin was taken from 28 weeks of pregnancy by a combined total of 1084 women.

Women taking metformin had reduced weight gain (mean difference -2.07 kg, 95% confidence interval -2.88 kg to -1.27 kg) and a reduced risk of hypertension (risk ratio: 0.56, 95% confidence interval 0.37-0.85) compared to those using insulin.

Neonates had a reduced risk of hypoglycemia (risk ratio: 0.63, 95% confidence interval 0.45-0.87) and reduced risk of large for gestational age (risk ratio: 0.80 95% confidence interval 0.64-0.99) compared to those whose mothers used insulin.

A small number of children exposed *in utero* to metformin in randomized controlled trials have been followed up for up to two years after birth. No significant differences in development compared to children exposed to insulin *in utero* were detected.

Dose

The metformin dose is the same as for non-pregnant women. Pharmacokinetic studies of metformin used to treat gestational diabetes indicate that an increase in dose may be needed to maintain glucose control as pregnancy progresses. The maximum dose studied in pregnancy was 2.5 g per day.

In randomized clinical trials of women taking metformin for gestational diabetes up to 46% of women did not achieve satisfactory glycaemic control with metformin alone and required additional insulin treatment. Women were more likely to need insulin treatment if they had a BMI greater than 31 kg/m² and fasting glucose greater than 5.2 mmol/L.

Lactation

In pharmacokinetic studies of mothers taking metformin, Infant exposure to metformin through breast feeding was low, less than 0.5% of the mother's weight adjusted dose. While this data suggests that breast-feeding does not expose the foetus to high concentrations of metformin, the decision to breast-feed should always be made as an individual benefit versus risk analysis.

4.7. Effects on ability to drive and use machines

Metformin monotherapy does not cause hypoglycemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycemia when metformin is used in combination with other antidiabetic agents, and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8. Undesirable effects

Metabolism and nutrition disorders

Very rare:

- Lactic acidosis (*see Section 4.4*) is a very rare (< 1/10,000) but serious metabolic complication that can occur due to metformin accumulation during treatment.
- A decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long-term with metformin.

Nervous system disorders

Common:

- Metallic taste (3%).

Gastrointestinal disorders

Very common:

- Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, 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.

However occurrence of gastrointestinal symptoms, once a patient is stabilized on any dose of metformin, could be due to lactic acidosis or other serious disease.

Hepatobiliary disorders

Very rare:

- Isolated reports of liver function test abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

Very rare:

- Mild erythema, pruritus and urticaria have been reported in some hypersensitive individuals but the incidence is very rare (< 1/10,000).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions

<https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Symptoms

Hypoglycemia 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 non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific 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 suspected in diabetic metformin treated patients with overdose. Lactic acidosis is diagnosed and monitored by measurement of serum electrolytes, arterial pH and pCO₂ 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 over alkalinisation with sodium bicarbonate. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excluding insulins, biguanides

ATC code: A10BA02

Mechanism of action

Metformin is an oral biguanide hypoglycemic agent. It 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 hypoglycemic 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 post-prandial blood glucose in diabetic patients but does not cause hypoglycemia in either diabetics or normal individuals.

Clinical efficacy and safety

The prospective randomized (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.

5.2. Pharmacokinetic properties

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 is nonlinear.

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.

Biotransformation

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

Elimination

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/min, renal clearance is reduced to 20% of normal.

5.3. Preclinical safety data

Carcinogenicity and mutagenicity

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 mg/kg/day and 1500 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.

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 test (mouse bone marrow).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Indoco Metformin 500mg and 850mg Tablets contain the following excipients:

- Colloidal silicon dioxide
- Hypromellose E-15
- Macrogol 6000
- Magnesium stearate
- Maize starch
- Povidone
- Propylene glycol
- Purified talc
- Purified water
- Sodium starch glycolate
- Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months from date of manufacture.

6.4. Special precautions for storage

Store at or below 30°C.

Protect from heat, light and moisture.

6.5. Nature and contents of container

Indoco Metformin 500mg Tablets are contained in PVC/PVdC/aluminum foil blister pack of 100 tablets.

Indoco Metformin 500mg Tablets: HDPE jar of 1000 tablets

Indoco Metformin 850mg Tablets are contained in PVC/PVdC/aluminum foil blister pack of 60 tablets.

Indoco Metformin 850mg Tablets: HDPE jar of 500 tablets

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Miro Healthcare Ltd
Hayes Knight, 5 William
Laurie Place
Auckland 0632
New Zealand
Phone: (09) 8874478

Distributor:
Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Mangere
AUCKLAND 2022

9. DATE OF FIRST APPROVAL

10 September 2009

10. DATE OF REVISION OF THE TEXT

22 Mar 2018

Summary table of changes

Sections changed	Summary of new information
All	Updated to the SPC format.
4.6	Replace the current wording in the pregnancy and breast-feeding section recommended by the MARC and Medsafe.
4.4, 4.5, 4.9, 5.1, 5.2, 5.3	Updated sections to align with market lead.
1,2,3,6.1,6.5	Change in medicine name
8	Change in Sponsor name, Distributor name
6.5	Update for addition of pack size
3	Change in description
1,2,3,6.1,6.5	Change in medicine name