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 Metformin500mg 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 sulfonylurea or insulin should be monitored by blood-sugar readings because combined therapy may cause hypoglycaemia. If it is decided to stabilise diabetic patients with metformin and insulin therapy, it is recommended that this is carried out in hospital because of the possibility of hypoglycaemia until the correct ratio of the two medicines is determined.

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 µg/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

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

4.3. Contraindications

Metformin is contraindicated in the following conditions:

- type 1/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*
- Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic ketoacidosis, diabetic precoma
- Renal failure (creatinine clearance <15 mL/minute 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 materials (see *Section 4.4*)

- Acute or chronic disease 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
- elective major surgery (see section 4.4)
- 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 (high mortality in the absence of prompt treatment) metabolic complication which can occur due to metformin accumulation. 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. Prompt haemodialysis is recommended to correct the acidosis and remove accumulated metformin (see section 4.9).

The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other separate risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

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 two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Decreased renal function in elderly subjects is frequent and asymptomatic.

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.

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.

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.

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

- 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.
- Periodic assessment of renal, hepatic and cardiovascular function is recommended during prolonged periods of treatment with metformin.
- Metformin hydrochloride alone does not cause hypoglycaemia; however, caution is advised when it is used in combination with other antidiabetic agents (sulphonylureas, glinides, insulin)
- 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.
- 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).

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 sections 4.3 and 4.4 have been taken into consideration, the dosage is frequently reviewed and the renal function is closely monitored.

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

Paediatric use

Metformin is not recommended for use in children.

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 clinical data in relation to the long-term effect of metformin on the development of skeletal and reproductive system in children and adolescents are not available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended.

Effects on Laboratory Tests

No information is available

4.5. Interaction with other medicines and other forms of interaction

Contraindicated combinations

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 section 4.4).

Inadvisable combinations

Alcohol: Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- Fasting or malnutrition
- Hepatic insufficiency

Avoid consumption of alcohol and alcohol-containing medications. Alcohol decreases blood glucose concentration by inhibiting hepatic glucose output, thus increasing the risk of hypoglycaemia and can also mask its warning symptoms. The CNS depressant effects of alcohol plus hypoglycaemia 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.

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.

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

ACE inhibitors: Co-administration of metformin and ACE inhibitors may result in a potentiation of the hypoglycaemic 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 glycaemic control is recommended.

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

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.

Organic cation transporters (OCT): Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with:

- Substrates/inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy.
- Substrates/inhibitors of OCT2 (such as cimetidine, dolutegravir, crizotinib, olaparib, daclatasvir, vandetanib) may decrease the renal elimination of metformin and thus lead to an increase metformin plasma concentration.

Carbonic anhydrase inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Metformin hydrochloride tablet may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

NSAIDs: May increase the risk of lactic acidosis and adversely affect renal function.

Therefore, caution is advised when these drugs are co-administered with metformin and a dose adjustment may be considered, particularly in patients with renal impairment.

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

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.

4.6. Fertility, pregnancy and lactation

4.7. 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 human daily dose on a body surface area basis

Pregnancy:

To date, no relevant epidemiological data is available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.

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 foetal 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.

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Australian Categorization Definition of Category C: 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.

Lactation

Metformin is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue breastfeeding or to discontinue metformin, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

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

4.8. Undesirable effects

The following undesirable effects may occur under treatment with metformin hydrochloride. Frequencies are defined as follows: very common: >1/10; common >1/100, <1/10; uncommon>1/1,000, <1/100; rare >1/10,000, <1/1,000; very rare <1/10,000; not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders

Common: Taste disturbance.

Gastrointestinal disorders

Very common: Gastrointestinal disorders such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Skin and subcutaneous tissue disorders

Very rare: Skin reactions such as erythema, pruritus and urticaria

Metabolism and nutrition disorders

Very rare:

- Lactic acidosis *(see Section 4.4).*
- Decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long-term with metformin. 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 should be considered (see Section 4.4)

Hepatobiliary disorders

Very rare: Isolated reports of liver function test abnormalities or hepatitis resolving upon metformin discontinuation.

In clinical trials in children and adolescents with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

Reporting suspected adverse reactions after authorisation 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 adverse 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 pCO_2 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 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood glucose lowering drugs, biguanides ATC code: A10BA02

Mechanism of action

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- Delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

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:

- 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).

Benefit regarding clinical outcome has not been shown for metformin hydrochloride used as secondline therapy, in combination with a sulfonylurea.

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.

Paediatrics
In a double blind, placebo-controlled study in 82 paediatric patients aged 10 to 16 years with type 2 diabetes (mean FPG 10.1 mmol/L), treatment with metformin (up to 2000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) resulted in a significant mean net reduction in FPG of 3.6 mmol/L, compared with placebo.

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.

Paediatrics

Following an oral dose, children 12 years and older, have shown similar pharmacokinetic profile of metformin to that observed in adults. Pharmacokinetic data in children between 10 and 12 years are not available

5.3 Preclinical safety data

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 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.

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 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

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9 DATE OF FIRST APPROVAL

10 September 2009

10 DATE OF REVISION OF THE TEXT

24 August 2023

Summary table of changes

Sections changed	Summary of new information
All	Updated to the SPC format.
4.2	Replace the current wording in Method of Administration, Combination with insulin or sulphonylureas in adults
4.3	Added Contraindications • Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
4.4	Replace the current wording in Lactic acidosis, Renal Impairment, added additional points in other precautions, special populations. Added effect on laboratory test
4.5	Added Combinations requiring precautions for use of organic cation transporters (OCT), Carbonic anhydrase inhibitors, NSAIDs
4.6	Replaced current wording in the pregnancy and Lactation section recommended by the MARC and Medsafe. Information on fertility is added
4.8	Replaced current wording in undesirable effects
5.1	Replace the current wording of Mechanism of action, elaborated more appropriately, information about Pediatrics added.
5.2	Added information about Pediatrics
8	Sponsors Phone number added