

# DATA SHEET

## METFORMIN GENERIC HEALTH

### *Metformin hydrochloride 500mg and 850mg tablets*

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

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### **Presentation**

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Metformin Generic Health tablets, 500mg: White to off white, round, bevelled edged biconvex film coated tablets with '500' embossed on one side. Available in blister packs of 100 tablets.

Metformin Generic Health tablets, 850mg: White to off white, round, bevelled edged biconvex film coated tablets with '850' embossed on one side. Available in blister packs of 60 tablets.

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### **Uses**

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#### ***Actions***

Metformin is a biguanide derivative producing an antihyperglycaemic effect in man only when there is insulin secretion. It causes hypoglycaemia only when used at a near lethal dose. Metformin has no effect on pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that it might potentiate the effects of insulin or that it might enhance the effect of insulin on peripheral receptor sites. This increased sensitivity seems to follow an increase in the number of insulin receptors on cell surface membranes. Other possible modes of action include inhibition of glucogenesis in the liver and delay in glucose absorption from the gastrointestinal tract.

Metformin may also lower levels of VLD-lipoprotein cholesterol and total cholesterol.

#### ***Pharmacokinetics***

Metformin absorption is relatively slow from the gastrointestinal tract with 50-60% being absorbed and may extend over about 6 hours. It is thought that absorption decreases as the dose increases. The drug is excreted in urine at a high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid, with a half-life varying between 1.7 and 3 hours. It is not bound to plasma proteins. The terminal elimination phase accounting for about 4 to 5% of the absorbed dose is slow with a half-life between 9 and

17 hours. Metformin is not metabolized. The main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady state ranges from about 1 to 2mcg/mL. In patients with significantly decreased renal function the plasma half-life of metformin is prolonged and renal clearance is decreased.

### ***Indications***

To control hyperglycaemia 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 sulphonylurea 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.

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## **Dosage and Administration**

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To minimise gastric intolerance such as nausea and vomiting, metformin should be taken with food.

The usual starting dose is one 500mg tablets three times daily. This dose or alternatively one 850mg tablet twice daily may be sufficient to provide good diabetic control. Control may be achieved within a few days but it is not unusual for the full effect not to occur for up to two weeks. If complete control is not achieved the dose may be gradually increased up to a maximum dose of 3g daily taken in divided doses. Once control has been achieved it may be possible to reduce the dosage without adverse effect.

When metformin therapy is used in conjunction with sulphonylurea or insulin therapy patients should have their blood-sugar levels monitored due to the possibility of hypoglycaemia occurring. It is recommended that patients requiring both metformin and insulin therapy should be stabilised in hospital until the correct ratio of the two medicines is determined.

### **Children:**

Metformin is not recommended for use in children.

### **Elderly:**

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

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## **Contraindications**

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Patients with a history of ketoacidosis with or without coma.

Significant renal impairment (serum creatinine levels  $\geq 136$ micromol/L (males),  $\geq 124$ micromol/L (females) or abnormal creatinine clearance).

Severe hepatic dysfunction.

Excessive alcohol intake either acute or chronic.

Cardiovascular collapse and in disease states associated with hypoxemia e.g. cardiorespiratory insufficiency which are often associated with hyperlactacidemia.

During stress conditions e.g. severe infections, trauma, or surgery or the recovery stage thereafter.

States associated with lactic acidosis e.g. shock or pulmonary insufficiency.

Patients with a history of lactic acidosis irrespective of the precipitating factors.

Patients suffering from severe dehydration.

Known hypersensitivity to metformin or any of the tablet excipients.

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## Warnings and Precautions

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The risk of lactic acidosis increases with the degree of renal dysfunction, impairment of creatinine clearance and the patient's age. Patients with serum creatinine levels above the upper limit of the normal range should not receive metformin. (See contraindications).

Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Patients should be warned against excessive alcohol intake either acute or chronic when taking metformin, since alcohol intake potentiates the effect of metformin on lactate metabolism.

Metformin should be temporarily discontinued 2 days prior to any intravascular radiocontrast study and not restarted until renal function has normalised.

It is prudent to discontinue metformin if any of the above conditions or stress conditions under Contraindications exist especially if gastrointestinal disturbances are noted or acidosis suspected. Therapy should only be resumed after lactic acidosis and ketoacidosis have been excluded.

Impairment of vitamin B<sub>12</sub> and folic acid absorption has been reported in some patients. Measurements of serum vitamin B<sub>12</sub> and folic acid are advisable on an annual basis for patients receiving long-term therapy.

Blood sugars should be monitored when patients are in catabolic states or receiving concomitant therapy with other hypoglycaemia agents.

Hypoglycaemia does not normally occur in patients receiving metformin alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose lowering agents e.g. sulphonylureas or ethanol.

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated haemoglobin levels. During initial dose titration, fasting glucose can be used to determine therapeutic response but thereafter both glucose and glycosylated haemoglobin should be monitored.

Initial and periodic monitoring of haematologic parameters e.g. haemoglobin/haematocrit and red blood cell indices and renal function should be performed on an annual basis.

### ***Use in Pregnancy and Lactation***

Category C. It is recommended that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Metformin was not teratogenic in rats and rabbits at doses of up to 600mg/kg/day. Determination of foetal concentrations has shown a partial placental barrier to metformin. However because animal studies are not always predictive of human response, the use of metformin during pregnancy is not recommended.

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

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## **Adverse Effects**

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Metformin is well tolerated with only minor, usually transient, gastrointestinal upsets. These can generally be avoided by taking metformin with meals or by a temporary lowering of the dose. Only about 3% of patients need to have metformin therapy withdrawn and it is important therefore that the treatment is not halted at the first signs of intolerance. These upsets usually disappear by the time the diabetes is controlled and do not return.

The most frequently reported adverse reactions are metallic taste in the mouth, epigastric discomfort, nausea and vomiting and rarely diarrhoea and anorexia.

Lactic acidosis has been reported with biguanides. It is a serious and often fatal metabolic complication which has been reported in a number of diseases including diabetes. It is characterised by acidosis (decreased blood pH), electrolyte disturbances with an increased anion gap, and an increased lactate level with altered lactate/pyruvate ratio. Azotaemia may also be present. In patients with a metabolic acidosis lacking evidence of ketoacidosis, lactic acidosis is a medical emergency which must be treated in hospital immediately. Physicians should instruct their patients to recognise the symptoms which could signal the onset of lactic acidosis. In the majority of fatal cases patients with early symptoms have not been investigated for lactic acidosis. The few cases of lactic acidosis

reported with metformin therapy have occurred in patients who had complications which are considered contraindications to the use of metformin. The problem of lactic acidosis with metformin is unusual provided that patients are correctly selected and attention is paid to the correct diet and dosage.

Mild erythema has been reported in some sensitive individuals but the incidence is rare and the effect is not serious with the rash resolving within several days without cessation of therapy.

Asymptomatic subnormal serum vitamin B<sub>12</sub> levels have been observed and 5 cases of megaloblastic anaemia have been reported. Serum vitamin B<sub>12</sub> levels should be monitored.

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## Interactions

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Certain drugs may potentiate the effect of metformin, particularly sulphonylurea type drugs used in the treatment of diabetes. Administration of these two types of drugs could produce a hypoglycaemic reaction, especially if they are given in patients already receiving other drugs such as long-acting sulphonamides, tuberculostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propranolol, which may potentiate the hypoglycaemic effect of the sulphonylurea.

Other drugs produce hyperglycaemia and may lead to a loss of blood sugar control. These include diuretics (thiazides, furosemide), corticosteroids, oral contraceptives (oestrogen plus progestogen), thyroid products and nicotinic acid in pharmacologic doses.

Elimination rate of the anticoagulant, phenprocumon, may increase by 20% when used concurrently with metformin. Patients receiving phenprocumon or other vitamin K anticoagulants should be monitored. An increase of prothrombin time may occur upon cessation of metformin therapy, with an increased risk of haemorrhage.

Cationic drugs e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin that are excreted by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such an interaction has been noted with the co-administration of cimetidine with metformin leading to reduced renal clearance of metformin, and therefore increased plasma metformin concentrations. Dose reductions should be considered in patients on cimetidine treatment.

Patients should be warned against using alcohol in excess while on metformin therapy since it may mask the outward signs of hypoglycaemia. Alcohol in a diabetic subject may cause an elevation of blood lactate. The combined effects of hypoglycaemia and the CNS depressant effect of alcohol may reduce the patient's ability to drive a motor vehicle and/or operate machinery.

Concomitant therapy with  $\beta$ -blockers may mask the external signs of hypoglycaemia e.g. tachycardia.

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## Overdosage

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## Symptoms:

Available information concerning treatment of a massive overdose of metformin is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhoea, drowsiness, weakness, dizziness, malaise and headache may be seen. Should these symptoms persist, lactic acidosis should be excluded. Hypoglycaemia has not been seen even with ingestion of up to 85g metformin although lactic acidosis has occurred in such circumstances. Hypoglycaemia may occur if excessive amounts of metformin are taken with a sulphonylurea, insulin or alcohol.

## Treatment:

Metformin should be discontinued and proper supportive therapy instituted. Metformin is dialysable with a clearance of up to 170mL/min under good haemodynamic conditions. Therefore haemodialysis may be useful for the removal of accumulated drug from patients in whom metformin overdose is suspected.

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## Storage

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Store below 30°C. Protect from heat, light and moisture.

Keep container tightly closed.

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## Medicine Classification

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Prescription Only Medicine

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## Package Quantities

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METFORMIN GENERIC HEALTH 500mg tablets:

Blister packs of 100 tablets.

METFORMIN GENERIC HEALTH 850mg tablets:

Blister packs of 60 tablets.

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## Supplier

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Douglas Pharmaceuticals Limited,  
P O Box 45 027,  
Lincoln,  
Auckland 0651

Telephone: (09) 835 0660

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**Date of Preparation**

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August 2009