NEW ZEALAND DATA SHEET

1. PRODUCT NAME (strength pharmaceutical form)

Metchek 500 mg, film-coated tablet, 500mg

Metchek 850 mg, film-coated tablet, 850mg

This product may not be interchangeable with other products containing Metformin hydrochloride in the New Zealand Market.

Not all tablet strengths maybe marketed.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name and strength of the active substance

Metformin hydrochloride 500 mg

Metformin hydrochloride 850 mg

Excipient(s) with known effect
<For the full list of excipients, see section 6.1.>

3. PHARMACEUTICAL FORM

Oral. Film-coated tablets

Presentations:
Metchek 500 mg: White to off-white, round bevelled edged biconvex film coated tablets with '500' debossed on one side and plain on the other side.
Thickness 6.2 ± 0.2 mm, diameter 11.0 ± 0.2 mm.

Metchek 850 mg: White to off-white, circular, bevelled edged biconvex film coated tablets.
Thickness 7.2 ± 0.2 mm, diameter 13.5 ± 0.2 mm.

Do not halve tablets. Dose equivalence when the tablets are divided has not been established.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 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

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 warnings and precautions).

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 (ie creatinine clearance greater than 120ml/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 stabilisation. Metformin will not produce a hypoglycaemic state when used alone, however, it increases insulin effectiveness

<u>Combination with insulin or sulphonyl ureas in adults</u>
Metformin therapy with a sulphonyl urea 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 until the correct ratio of the two medicines is determined because of the possibility of hypoglycaemia.

<u>Elderly</u>
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 daily 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 <15mL/min) (see contraindications).

Metformin may be used in patients with stable renal impairment (but see warnings and precautions). Where possible the dose should be titrated with gradual dose increments.

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

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

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

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

Children

Metformin is not recommended for use in children.

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
- 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 Warnings and Precautions)
- 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.

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 contraindications) Hepatic dysfunction is also a risk as lactate clearance is reduced (see contraindications). 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 contraindications).

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 μg/mL (5mg/L) are generally found (see Pharmacokinetics).

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 dyspnoea, and coma. Lactic acidosis is characterised by acidosis (decreased blood pH), elevated lactate levels above 5mmol/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 hospitalised immediately. Prompt haemodialysis is recommended to correct the acidosis and remove accumulated metformin (see overdose).

Renal Impairment

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 (see Dosage and Administration). 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 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.

Prompt haemodialysis is recommended to correct the acidosis and remove accumulated metformin (see overdose)

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 an NSAID.

Metformin is contraindicated in patients with creatinine clearance below 15mL/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 contraindications) and used with caution in patients with milder disease.

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 Contraindications and Warning and Precautions have been taken into consideration, the dosage is frequently reviewed and the renal function is closely monitored.

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 anaesthesia. 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.

4.5 Interaction with other medicines and other forms of interaction

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 acidin 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 excretedby renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such aninteraction 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 ß-blockers mask the external signs of hypoglycaemia e.g. tachycardia.

4.6 Use in Pregnancy and Lactation

Category C.

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 fetus 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 fetus. Metformin was not teratogenic in rats and rabbits at doses of up to 600mg/kg/day. However, *In vitro* tests investigating genotoxicity and embryotoxicity have suggested that metformin may have weak toxic effects.
Data are available from a meta-analysis of randomised 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 hypoglycaemia (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 randomised 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 randomised 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/m^2 and fasting glucose greater than 5.2 mmol/L.

Breastfeeding
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 fetus to high concentrations of metformin, the decision to breast-feed should always be made as an individual benefit versus risk analysis.

Fertility
There is no fertility data available

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.

4.8 Undesirable effects

Gastrointestinal disorders
Very common: Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, 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 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 Warnings and Precautions) 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 .

Skin and subcutaneous tissue disorders
Very rare: Mild erythema, pruritus and urticaria have been reported in some hypersensitive individuals.

Nervous system disorders
Common: Metallic taste (3%).

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

Reporting of suspected adverse reactions
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:
Available information concerning treatment of a massive over dosage 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. Hypoglycaemiamay 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.

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

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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch Glycollate, Povidone, Maize starch, Magnesium stearate,
Silica, colloidal anhydrous, Hypromellose, Macrogol, Purified talc, Titanium dioxide.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

60 months when stored at or below 25°C

6.4 Special precautions for storage

Store below 25°C. Protect from heat, light and moisture. Keep container tightly closed.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Metchek 500 mg tablets: HDPE jar of 500 tablets and HDPE bottle of 1000 tablets.
Metchek 850 mg tablets: HDPE jar of 250 tablets and HDPE bottle of 500 tablets.
Not all tablet strengths or pack sizes maybe marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements <for disposal>.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

PSM Healthcare Limited, t/a API Consumer Brands
14-16 Norman Spencer Drive

PO Box 76 401
Manukau City
AUCKLAND 2241
Telephone 0508 776746

9. DATE OF FIRST APPROVAL

26/11/2009

10. DATE OF REVISION OF THE TEXT

April 2017

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
All sections	Update to the SPC-style format effective 1/03/2017.
4.6	September 2016 Medicines Adverse Reactions Committee (MARC) reviewed risks and benefits of metformin treatment in pregnancy. Minutes of meeting published on Medsafe website (www.medsafe.govt.nz/profs/adverse/Minutes160.htm#3.2.1). MARC considered that there is an increasing amount of evidence regarding use of metformin in pregnancy, particularly for gestational diabetes. MARC considered that this information should be included in the data sheets for metformin to better help inform treatment choices in gestational diabetes. Medsafe request to update datasheet Section 'Use in Pregnancy and Lactation' (letter 18/10/2016).