

# NEW ZEALAND DATA SHEET

## METFORMIN MYLAN



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### 1. Product Name

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Metformin Mylan, 500 mg, 850 mg & 1000 mg, film coated tablet

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### 2. Qualitative and Quantitative Composition

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Each film coated tablet contains 500 mg, 850 mg or 1000 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

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### 3. Pharmaceutical Form

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Metformin Mylan 500 mg: White, round, normal convex, film coated tablet, plain on both sides.

Metformin Mylan 850 mg: White, round, normal convex, film coated tablet, plain on both sides.

Metformin Mylan 1000 mg: White, oval, film coated tablet, debossed "MF" and "3" on either side of the break line on one side and "G" on the other side.

Do not halve the 500 mg and 850 mg tablets. Dose equivalence when the tablet is divided has not been established.

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### 4. Clinical Particulars

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#### 4.1 *Therapeutic indications*

- Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.
- Metformin may be used as initial treatment or in sulfonylurea failures either alone or in combination with a sulfonylurea and other oral agents.
- Adjuvant therapy in insulin dependent diabetes especially if 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 section 4.4).**

#### **Dose**

#### ***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.

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The maximum dose of 3 g daily should only be used in patients with good renal function (i.e. 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 stabilisation. Metformin will not produce a hypoglycaemic state when used alone, however, it increases insulin effectiveness

### ***Combination with insulin or sulfonylureas 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**

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 500 mg.

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 15 mL/min metformin must be discontinued.

#### **Debilitated or malnourished patients**

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

#### **Paediatric**

Metformin is not recommended for use in children.

#### **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
- 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.

#### **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 µg/mL (5 mg/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 characterised 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 hospitalised immediately. Prompt haemodialysis is recommended to correct the acidosis and remove accumulated metformin (see section 4.9).

##### **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 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 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 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 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.

### **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.

### **Heart failure**

Type 2 diabetic patients with heart failure are at an increased risk of hypoperfusion 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 B<sub>12</sub> levels because of reports of decreased vitamin B<sub>12</sub> absorption.

## 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<sub>max</sub> and AUC by 20 and 9%, respectively, and increased the amount of metformin excreted in the urine. T<sub>max</sub> and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on the pharmacokinetics of nifedipine.

### Pharmacodynamic interactions

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

**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, 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 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.

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

**Corticosteroids:** Corticosteroids tend to produce hyperglycaemia and may lead to loss of control.

**Alcohol:** 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.

**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 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 600 mg/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<sup>2</sup> and fasting glucose greater than 5.2 mmol/L.

#### **Breast-feeding**

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**

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.

### **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 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 B<sub>12</sub> 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 but the incidence is very rare (< 1/10,000).

#### **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 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**

Hypoglycaemia has not been seen with ingestion of up to 85 g of metformin alone, although lactic acidosis has occurred in such circumstances. The onset of lactic acidosis is often subtle and accompanied only by 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<sub>2</sub> and arterial lactate plasma level.

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

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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## 5. Pharmacological Properties

### 5.1 *Pharmacodynamic properties*

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

#### Mechanism of action

Metformin is an oral biguanide hypoglycaemic 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 hypoglycaemic 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 hypoglycaemia in either diabetics or normal individuals.

#### Clinical efficacy and safety

A clinical 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.

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 µg/mL. During controlled clinical trials, maximum metformin plasma levels did not generally exceed 5 µg/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.

### **Linearity/non-linearity**

It is assumed that the pharmacokinetics of metformin absorption are non-linear.

## **5.3 Preclinical safety data**

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 tumourigenic 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).

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## **6. Pharmaceutical Particulars**

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### **6.1 List of excipients**

Magnesium stearate, povidone, and a coating containing hypolose, hypromellose and macrogols.

Metformin Mylan is gluten and lactose free.

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years.

## **6.4 Special precautions for storage**

Store at or below 25°C.

## **6.5 Nature and contents of container**

500 mg tablets: HDPE bottle with polypropylene screw cap. Pack-sizes of 30, 100, 500 and 1000 tablets.

850 mg tablets: HDPE bottle with polypropylene screw cap. Pack-sizes of 30, 100, 250, 500 and 1000 tablets.

1000 mg tablets: HDPE bottle with polypropylene cap. Pack-sizes of 30, 100, 500 and 1000 tablets.

Not all pack types and sizes may be marketed.

## **6.6 Special precautions for disposal**

Not applicable.

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## **7. Medicines Schedule**

Prescription Medicine

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## **8. Sponsor Details**

Mylan New Zealand Ltd  
PO Box 11183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792

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## **9. Date of First Approval**

10 July 2014      Metformin Mylan 500 mg and 850 mg film coated tablets

21 September 2017      Metformin Mylan 1000 mg film coated tablets

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## **10. Date of Revision of the Text**

21 September 2017      Addition of 1000 mg strength