SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

MYLAN METFORMIN 500 Film-coated tablets

MYLAN METFORMIN 850 Film-coated tablets

MYLAN METFORMIN 1000 Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MYLAN METFORMIN 500 film-coated tablets contain metformin hydrochloride 500 mg.

Sugar free.

MYLAN METFORMIN 850 film-coated tablets contain metformin hydrochloride 850 mg.

Sugar free.

MYLAN METFORMIN 1000 film-coated tablets contain metformin hydrochloride 1 000 mg.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

MYLAN METFORMIN 500: White, round, biconvex, film-coated tablets.

MYLAN METFORMIN 850: White, round, biconvex, film-coated tablets.

MYLAN METFORMIN 1000: 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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MYLAN METFORMIN is indicated for:

Adults

- Treatment of type II diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise do not result in adequate glycaemic control.
- MYLAN METFORMIN can be given alone as initial therapy, or can be administered in combination

with other oral antidiabetic medicines or with insulin.

Children and adolescents

MYLAN METFORMIN may be used as monotherapy or in combination with insulin in children over 12 years of age and adolescents with type II diabetes.

4.2 Posology and method of administration

Posology

It is important that MYLAN METFORMIN tablets be taken in divided doses with meals.

Adults

- Initially one 500 mg tablet two to three times a day, or one 850 mg or 1 000 mg tablet twice a day, with or after food.
- After 10 to 15 days the dose should be adjusted according to blood glucose measurements. A slow increase in dose may improve gastrointestinal tolerability.
- Good diabetic control may be achieved within a few days, but it is not unusual for the full effect to be delayed for up to two weeks.
- If control is incomplete, a cautious increase in dosage to a maximum of 2 550 mg daily is justified. Once control has been obtained, it may be possible to reduce the dosage of MYLAN METFORMIN.

Special populations

Elderly population

MYLAN METFORMIN dose in the elderly should be adjusted based on renal function.

Combination therapy

See section 4.4.

Children and adolescents

- MYLAN METFORMIN can be used in children from 12 years of age and adolescents.
- The usual starting dose is 500 mg or 850 mg once daily, given during meals or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements.
- A slow increase of dose may improve gastrointestinal tolerability.
- The maximum recommended dose of metformin is 2 000 mg daily, taken as 2 or 3 divided doses.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to metformin or any of the excipients of MYLAN METFORMIN tablets.
- Diabetic ketoacidosis, diabetic pre-coma, or a history thereof.
- Impaired renal function (creatinine clearance ≤ 60 mL/min).
- Acute conditions with the potential to alter renal function such as:
  - Dehydration.
  - Severe infection.
  - Shock.
  - Intravascular administration of iodinated contrast medicines (see section 4.4).
- Acute or chronic disease which may cause tissue hypoxia such as:
  - Cardiac or respiratory failure.
  - Recent myocardial infarction.
  - Shock.
  - Pancreatitis.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Pregnancy and lactation (see section 4.6).
- Children under 12 years of age as safety and efficacy have not been established (see section 4.4).

4.4 Special warnings and precautions for use

Lactic acidosis

- Lactic acidosis is associated with the use of MYLAN METFORMIN.
- Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment) metabolic complication which most often present at acute worsening of renal function or cardiorespiratory illness or sepsis that can occur due to metformin accumulation.
- The incidence of lactic acidosis may be reduced by assessing also other associated risk factors such as poorly controlled diabetes mellitus type 2, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

- In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), MYLAN METFORMIN should be temporarily discontinued and contact with a doctor is recommended.
- Medicines that can acutely impair renal function (such as antihypertensives, diuretics and non-steroidal anti-inflammatory drugs (NSAIDs)) should be initiated with caution in MYLAN METFORMIN-treated patients.
- In patients presenting with a metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected, and therapy stopped. Lactic acidosis is a medical emergency, which must be treated in hospital. MYLAN METFORMIN is excreted by the kidneys and regular monitoring of renal function is advised in all diabetics.
- Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings include decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, MYLAN METFORMIN should be discontinued, and the patient should be hospitalised immediately.

Renal function

- As MYLAN METFORMIN is excreted by the kidneys, serum creatinine levels 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 subjects.
- Decreased renal function in elderly subjects is frequent and may be asymptomatic.
- 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 NSAID's (see section 4.3).

Cardiac function

- Patients with heart failure are more at risk of hypoxia and renal insufficiency.
- For patients with acute and unstable heart failure, MYLAN METFORMIN is contraindicated (see section 4.3).

Administration of iodinated contrast medicines

As the intravascular administration of iodinated contrast materials in radiological studies can lead to

renal failure, MYLAN METFORMIN should be discontinued prior to, or at the time of the test and not re-instituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery

- MYLAN METFORMIN should be discontinued 48 hours before elective surgery with general anaesthesia and should not be resumed earlier than 48 hours afterwards.
- MYLAN METFORMIN therapy should be stopped 2 – 3 days before surgery and before clinical investigations such as intravenous urography and intravenous angiography, and reinstated only after control of renal function has been regained.

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.
- In combination with insulin or other oral antidiabetics; hypoglycaemia can occur.
- The use of MYLAN METFORMIN is not advised in conditions which may cause dehydration or in patients suffering from serious infections, trauma or on low calorie intake.
- Patients on long-term treatment with MYLAN METFORMIN should have an annual estimation of vitamin B12 levels, since MYLAN METFORMIN may cause malabsorption of vitamin B12 and folic acid which may result in megaloblastic anaemia.
- During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combined therapy may cause hypoglycaemia.
- Stabilisation of diabetic patients with MYLAN METFORMIN and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been obtained.
- Contraindications should be carefully observed.

Children over the age of 12 years and adolescents

- The diagnosis of type II diabetes mellitus must be confirmed before treatment with MYLAN METFORMIN is started.

- No effect on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available.
- Careful follow-up on the effect of MYLAN METFORMIN on these parameters is recommended, especially in pre-pubescent children.

4.5 Interaction with other medicines and other forms of interaction

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.

Iodinated contrast medicines

- Intravascular administration of iodinated contrast medicines may lead to renal failure, resulting in MYLAN METFORMIN accumulation and a risk of lactic acidosis.
- MYLAN METFORMIN should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use

Some medicines can adversely affect renal function, which may increase the risk of lactic acidosis e.g. NSAID's, including selective cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such medicines in combination with MYLAN METFORMIN, close monitoring of renal function is necessary.

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics

- Have intrinsic hyperglycaemic activity.
- Medical practitioners should inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of MYLAN METFORMIN during therapy with the other medicine and upon its discontinuation.

Organic Cation Transporters (OCT)

- Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of MYLAN METFORMIN with:
  - Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
  - Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
  - Inhibitors of OCT2 (such as dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
  - Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.
- Caution is therefore advised, especially in patients with renal impairment, when these medicines are co-administered with MYLAN METFORMIN, as metformin plasma concentration may increase. If needed, dose adjustment of MYLAN METFORMIN may be considered as OCT inhibitors/inducers may alter the efficacy of MYLAN METFORMIN.

ACE-inhibitors

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of MYLAN METFORMIN, during therapy with the other medicine, and upon its discontinuation.

Cimetidine

Reduced renal clearance of MYLAN METFORMIN has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants

- MYLAN METFORMIN has been reported to diminish the activity of warfarin.
- Therefore, close monitoring of INR should be considered.

Sulphonylurea

Concomitant therapy of MYLAN METFORMIN with sulphonylurea may cause hypoglycaemia.

Vitamins

- Long-term treatment with MYLAN METFORMIN may cause vitamin B12 and folic acid malabsorption in the gastrointestinal tract, thus a dose reduction of MYLAN METFORMIN should be considered (see section 4.4).

- Patients on long-term MYLAN METFORMIN treatment should have full blood counts at regular intervals (at least twice annually) and if megaloblastic anaemia is diagnosed, they should receive vitamin B12.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

When the patient plans to become pregnant diabetes should not be treated with MYLAN METFORMIN.

Pregnancy

The use of MYLAN METFORMIN during pregnancy is contraindicated as the safety in pregnancy and lactation has not been established.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with MYLAN 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.

Breastfeeding

Metformin, as contained in MYLAN METFORMIN, crosses the placenta and is distributed into breast milk in small amounts. Patients using MYLAN METFORMIN should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

MYLAN METFORMIN may have no or negligible influence on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision. Patients should be alerted to the risk of hypoglycaemia when MYLAN METFORMIN is used in combination with other antidiabetic medicines.

4.8 Undesirable effects

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	**Less frequent**	**Frequency not known**

Blood and the lymphatic system disorders			Megaloblastic anaemia.
Immune system disorders	Hypersensitivity.		
Metabolism and nutrition disorders	Decrease in vitamin B_{12}	Decrease in folic acid absorption, lactic acidosis, hypoglycaemia (see section 4.4).	
Nervous system disorders	Taste disturbance.		
Gastrointestinal disorders	Anorexia, nausea, vomiting, constipation, diarrhoea, abdominal pain, metallic taste, 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 MYLAN METFORMIN be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also		

	improve gastrointestinal tolerability.		
Hepatobiliary disorders		Severe cholestatic hepatitis, liver function abnormalities or hepatitis resolving upon metformin discontinuation.	
Skin and subcutaneous tissue disorders		Erythema, pruritus, urticaria.	
Renal and urinary disorders			Ketoacidosis, ketonuria.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA on the SAHPRA website at: https://medsafety.sahpra.org.za/#download1, via email at: adr@sahpra.org.za or via telephone at: 0125010311.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Symptoms of overdosage:

- Hypoglycaemia can occur when MYLAN METFORMIN is given concomitantly with other oral antidiabetics, insulin or alcohol.
- In excessive dosage, and particularly if there is a possibility of accumulation, lactic acidosis may develop.
- Lactic acidosis is a medical emergency and must be treated in hospital.

Treatment of overdosage:

- Intensive symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels.
- There is no specific antidote for overdose with MYLAN METFORMIN.
- Treatment is supportive and symptomatic and should be directed at fluid loss and metabolic disturbances.
- The most effective method to remove lactate and MYLAN METFORMIN is haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2 Oral hypoglycaemics

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides; ATC code: A10BA02

Metformin is a biguanide oral anti-hyperglycaemic medicine.

Its mode of action is thought to be increased peripheral glucose utilisation mediated by increased insulin sensitivity and inhibition of increased hepatic and renal gluconeogenesis.

5.2 Pharmacokinetic properties

Absorption

After an oral dose of metformin, T_{max} is reached in 2,5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50 – 60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20 – 30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

Steady state plasma concentrations are reached within 24 to 48 hours.

Food decreases the extent and slightly delays the absorption of metformin; following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC (area under the curve) and a 35-minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these changes is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak

concentration is lower than the plasma peak concentration and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution ranged between 63 – 276 L.

Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6,5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Paediatrics

After single doses of metformin 500 mg in paediatric patients, they have shown a similar pharmacokinetic profile to that observed in healthy adults.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MYLAN METFORMIN 500 and MYLAN METFORMIN 850:

Povidone K-30, magnesium stearate.

Film-coating: Hydroxypropyl methyl cellulose

OR

Opadry clear 20C59060 (composition: hypromellose 6 cP, hydroxypropyl cellulose, hypromellose 15 cP, macrogol 400, macrogol 8000).

MYLAN METFORMIN 1000:

Povidone K-30, magnesium stearate.

Film-coating: Opadry clear 20C59060 (composition: hypromellose 6 cP, hydroxypropyl cellulose, hypromellose 15 cP, macrogol 400, macrogol 8000).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

MYLAN METFORMIN 500, MYLAN METFORMIN 850 and MYLAN METFORMIN 1000: 36 months in securitainers.

MYLAN METFORMIN 850 and MYLAN METFORMIN 1000: 36 months in blister packs.

MYLAN METFORMIN 500: 24 months in blister packs.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Blisters to be kept in the outer carton until required for use.

6.5 Nature and contents of container

MYLAN METFORMIN 500:

White opaque high-density polyethylene (HDPE) bottle with white opaque polypropylene (PP) cap in pack sizes of 56, 84, 90, 100 or 500 tablets.

Blister pack comprising of clear transparent PVC film with backing of aluminium foil coated with heat seal lacquer. Blister strips of 14 tablets packed into unit cartons of 56 or 84 tablets. Blister strips of 15 tablets packed into unit cartons of 90 tablets.

MYLAN METFORMIN 850:

White opaque high-density polyethylene (HDPE) bottle with white opaque polypropylene (PP) cap in pack sizes of 60, 84 or 300 tablets.

Blister pack comprising of clear transparent PVC film with backing of aluminium foil coated with heat seal lacquer. Blisters strips of 14 tablets are packed into unit cartons of 28, 56 or 84 tablets. Blister strips of 15 tablets packed into unit cartons of 60 tablets.

MYLAN METFORMIN 1000:

White opaque high-density polyethylene (HDPE) bottle with white opaque polypropylene (PP) cap in pack sizes of 30, 100 or 1 000 tablets.

Blister pack comprising of clear transparent PVC film with backing of aluminium foil coated with heat seal lacquer. Blisters are packed in an outer carton in pack sizes of 56, 60, 100 or 300 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

8 REGISTRATION NUMBERS

MYLAN METFORMIN 500: 33/21.2/0204

MYLAN METFORMIN 850: 33/21.2/0205

MYLAN METFORMIN 1000: 45/21.2/0669

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MYLAN METFORMIN 500: 13 December 2000

MYLAN METFORMIN 850: 13 December 2000

MYLAN METFORMIN 1000: 10 April 2014

10 DATE OF REVISION OF THE TEXT

09 March 2023