Applicant: Teva Pharmaceuticals (Pty) Ltd	Product: METFORMIN TEVA ER 500 METFORMIN TEVA ER 750 METFORMIN TEVA ER 1000
Registration Nos.: 53/21.2/0227-9	**Dosage Form:** Extended release tablet **Strength:** 500 mg, 750 mg & 1000 mg, respectively.

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

METFORMIN TEVA ER 500, Extended Release Tablets

METFORMIN TEVA ER 750, Extended Release Tablets

METFORMIN TEVA ER 1000, Extended Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Extended Release Tablet contains 500 mg, 750 mg or 1000 mg metformin hydrochloride.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Extended Release Tablets.

METFORMIN TEVA ER 500: White to off-white, capsule shaped tablet debossed with ‘SR 500’ on one side and plain on other side.

METFORMIN TEVA ER 750: White to off-white, capsule shaped tablet debossed with ‘SR 750’ on one side and plain on other side.

METFORMIN TEVA ER 1000: White to off-white, oval tablet debossed with ‘SR 1000’ on one side and plain on other side.

4 CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control. METFORMIN TEVA ER can be given alone as initial therapy or can be administered in combination with other oral antidiabetic medicines or with insulin.

4.2 Posology and method of administration:

METFORMIN TEVA ER 500: The usual starting dose is one tablet daily given with the evening meal. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dosage is 4 tablets daily. Dosage increases should be made in increments of 500 mg every 10 to 15 days, up to a maximum of 2000 mg once daily with an evening meal. If glycaemic control is not achieved with METFORMIN TEVA ER 500 4 tablets once daily, METFORMIN TEVA ER 500 2 tablets twice daily should be considered, with both doses given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

METFORMIN TEVA ER 750: The usual starting dose is one tablet daily given with the evening meal. 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 recommended dosage is 2 tablets once daily, with the evening meal. If glycaemic control is not achieved with METFORMIN TEVA ER 750 2 tablets once daily, METFORMIN TEVA ER 750 may be increased to a maximum dose of 3 tablets once daily with the evening meal. If glycaemic control is not achieved on METFORMIN TEVA ER 750 3 tablets once daily, one tablet of METFORMIN TEVA ER 750 in the morning and two tablets of METFORMIN TEVA ER 750 in the evening should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

METFORMIN TEVA ER 1000: METFORMIN TEVA ER 1000 is intended as maintenance therapy for patients already treated with either 1000 mg (2 tablets of METFORMIN TEVA ER 500) or 2000 mg (4 tablets of METFORMIN TEVA ER 500) of sustained release metformin hydrochloride. If glycaemic control is not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum daily dose of 3000 mg daily.

Switching patients already treated with metforrnin tablets: In patients already treated with metformin tablets, the starting dose of METFORMIN TEVA ER prolonged release tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients' treated with metformin at a dose above 2000 mg daily, switching to METFORMIN TEVA ER prolonged release tablets is not recommended. Switching patients from other oral antidiabetic medicines: If transfer from another oral antidiabetic medicine, is intended, discontinue the other and initiate METFORMIN TEVA ER prolonged release tablets at the doses indicated above.

Combination therapy with insulin: METFORMIN TEVA ER prolonged release tablets and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is METFORMIN TEVA ER 500 once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, switch to METFORMIN TEVA ER 1000 may be considered.

Other combination therapy: See **section 4.4**.

Special populations:

Elderly: Due to the potential for decreased renal function in elderly subjects, the dosage for the METFORMIN TEVA ER range should be adjusted based on renal function. Regular assessment of renal function is necessary (See **section 4.4**)

Children: In the absence of available data, the METFORMIN TEVA ER range should not be used in children.

4.3 Contraindications:

- Hypersensitivity to metformin or to any of the excipients listed in **section 6.1**.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Renal failure or renal dysfunction (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 media.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as:
    - heart failure
    - respiratory failure
    - pancreatitits
    - recent myocardial infarction
    - shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- The use of METFORMIN TEVA ER during pregnancy is not advised.

4.4 Special Warnings and Precautions for Use:

Lactic acidosis:

Lactic acidosis, a very rare, but serious, metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin as contained in METFORMIN TEVA ER accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), METFORMIN TEVA ER should be temporarily discontinued and contact with a healthcare provider is recommended.

Medicines that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in METFORMIN TEVA ER treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicines that may cause lactic acidosis (see **sections 4.3** and **4.5**).

Patients and/or care givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking METFORMIN TEVA ER and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7,35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function:

GFR should be assessed before treatment initiation and regularly thereafter. METFORMIN TEVA ER is contraindicated in patients with GFR < 60 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see **section 4.3**.

Serum creatinine levels should also be determined before initiating treatment with METFORMIN TEVA ER, 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 patients are frequent and 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 a NSAID.

METFORMIN TEVA ER therapy should be stopped 2 to 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.

The use of METFORMIN TEVA ER formulations 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 METFORMIN TEVA ER should have an annual estimation of vitamin B12 levels, since METFORMIN TEVA ER may cause malabsorption of vitamin B12, which may result in megaloblastic anaemia.

Cardiac function:

Patients with heart failure are more at risk of hypoxia and renal insufficiency.

METFORMIN TEVA ER is contraindicated in patients with heart failure, (see **section 4.3**).

Elderly:

Due to the potential for decreased renal function in elderly subjects, the dosage for METFORMIN TEVA ER should be adjusted based on renal function. Regular assessment of renal function is necessary.

Serum creatinine levels should be determined before initiating treatment and at least two to four times a year in elderly patients.

Decreased renal function in elderly patients is frequent and 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 a NSAID.

Administration of iodinated contrast medicines:

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. METFORMIN TEVA ER should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see **sections 4.2** and **4.5.**

Surgery:

METFORMIN TEVA ER must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

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 order to avoid hypoglycaemia, caution is advised when METFORMIN TEVA ER is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

The use of METFORMIN TEVA ER formulations 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 METFORMIN TEVA ER formulations should have an annual estimation of vitamin B12 levels, since METFORMIN TEVA ER range may cause malabsorption of vitamin B12, which may result in megaloblastic anaemia.

During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combination therapy may cause hypoglycaemia. Stabilisation of diabetic patients with METFORMIN TEVA ER and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been obtained.

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

4.5 Interaction with other medicines and other forms of interaction:

Concomitant use not recommended:

Alcohol:

There is an increased risk of lactic acidosis in acute alcohol intoxication, particularly in the case of fasting or malnutrition, and hepatic insufficiency. Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast medicines:

Intravascular administration of iodinated contrast agents may lead to accumulation of METFORMIN TEVA ER and a risk of lactic acidosis.

METFORMIN TEVA ER must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see **sections 4.2** and **4.4**.

Combinations requiring precautions for use:

Anticoagulants:

METFORMIN TEVA ER may diminish the activity of warfarin, dose adjustments and increased frequency of INR determinations should be considered.

Sulphonylurea:

Concomitant therapy of METFORMIN TEVA ER with sulphonylurea may cause hypoglycaemia.

Vitamins:

Long term treatment with METFORMIN TEVA ER may cause vitamin B12 mal-absorption in the gastro-intestinal tract, thus a dose reduction of METFORMIN TEVA ER should be considered.

Some medicines can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with METFORMIN TEVA ER, close monitoring of renal function is necessary.

Medicines with intrinsic hyperglycaemic activity [e.g. glucocorticoids (systemic and local routes) and sympathomimetics].

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the METFORMIN TEVA ER dosage 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 METFORMIN TEVA ER with:

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of METFORMIN TEVA ER.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of METFORMIN TEVA ER.
- Inhibitors of OCT2 (such as cimetidine, 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 TEVA ER.

Caution is therefore advised, especially in patients with renal impairment, when these medicines are co-administered with METFORMIN TEVA ER, as metformin plasma concentration may increase. If needed, dose adjustment of METFORMIN TEVA ER may be considered as OCT inhibitors/inducers may alter the efficacy of METFORMIN TEVA ER.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

The use of METFORMIN TEVA ER during pregnancy is not advised (see **section 4.3**).

Breastfeeding:

METFORMIN TEVA ER is excreted into human breast milk. Breastfeeding is not recommended during METFORMIN TEVA ER treatment.

Fertility:

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

4.7 Effects on ability to drive and use machines:

METFORMIN TEVA ER 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 TEVA ER is used in combination with other antidiabetic medicines (e.g. sulphonylureas, insulin, or meglinitides).

4.8 Undesirable effects:

During treatment initiation, the most frequent adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

Metabolism and nutrition disorders:

Frequent:

Decrease of vitamin B12 absorption with decrease of serum levels during long term use of METFORMIN TEVA ER.

Less frequent:

Lactic acidosis (see **section 4.4**). Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders:

Frequent:

Taste disturbance.

Gastrointestinal disorders:

Frequent:

Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastro-intestinal tolerability.

Hepato-biliary disorders:

Less frequent:

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon METFORMIN ER discontinuation.

Skin and subcutaneous tissue disorders:

Less frequent:

Skin reactions such as erythema, pruritus, urticaria.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose:

Hypoglycaemia can occur when METFORMIN TEVA ER is given concomitantly with a sulphonylurea, insulin or alcohol. In excessive dosage, and particularly if there is a possibility of accumulation, lactic acidosis may develop. Intense symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels.

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of METFORMIN TEVA ER may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

Treatment of overdosage:

There is no specific antidote for overdose with METFORMIN TEVA ER. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances. Haemodialysis is the most effective way to remove lactate and metformin.

5 PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A 21.2 Oral hypoglycaemics.

ATC code: (A10BA02: Gastrointestinal tract and metabolism)

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.

Mechanism of action:

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 and 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).

5.2 Pharmacokinetic properties:

Absorption:

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2,5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of metformin prolonged release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets twice daily.

Intra-subject variability of C_{max} and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30 % (both C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000 mg of metformin as prolonged release tablets.

Following a single oral administration of 1500 mg of METFORMIN TEVA ER 750, a mean peak plasma concentration of 1193 ng/mL is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Following a single oral administration in the fed state of one tablet of METFORMIN TEVA ER 1000, a mean peak plasma concentration of 1214 ng/mL is achieved with a median time of 5 hours (range of 4 to 10 hours).

When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77 % (C_{max} is increased by 26 % and T_{max} is slightly prolonged by about 1 hour).

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63 to 276 L.

Biotransformation:

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.

Characteristics in specific groups of patients:

Renal impairment:

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see **section 4.2**).

5.3 Preclinical safety data:

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6 PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Intragranular and extragranular:

Carmellose sodium

Hypromellose

Magnesium stearate

Silica colloidal anhydrous

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

3 years

6.4 Special precautions for storage:

Store at or below 25 °C in the original package.

Do not remove blister from carton until required for use.

6.5 Nature and contents of container:

METFORMIN TEVA ER 500, 750 & 1000 Extended Release Tablets are packed in blister of 10 tablets (packed in foil blister aluminium 0,02 mm x 198 mm plain & PVC film 0,35 mm x 202 mm transparent) and 6 blisters per carton.

The blisters are packed in secondary packaging material: outer cardboard carton.

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. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8 REGISTRATION NUMBER:

METFORMIN TEVA ER 500: 53/21.2/0227

METFORMIN TEVA ER 750: 53/21.2/0228

METFORMIN TEVA ER 1000: 53/21.2/0229

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

30 March 2021

10. DATE OF REVISION OF THE TEXT:

24 August 2026