APPROVED SPC

For

Tendiap MR 60 mg

Registration No.: 43/21.2/0959

Date Approved: May 2020

Confidential Information

Tendiap MR 60 mg

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Tendiap MR 60 mg, modified release tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablet contains 60 mg of gliclazide.

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release tablet.

Tendiap MR 60 mg: White, oblong, tablet, 15 mm long and 7 mm wide, scored and engraved, with 'DIA 60' on both faces.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In Type 2 diabetic patients, in association with dietary measures, life-style changes and exercise, when dietary measures, life-style and exercise alone are not sufficient to control blood glucose.

4.2 Posology and method of administration

Posology

For adult use only

The daily dose may vary from one half to 2 tablets a day, i.e. 30 to 120 mg taken as a single daily dose. It is recommended that **Tendiap MR 60 mg** be taken with breakfast.

If a dose is forgotten, the dose taken on the next day should not be increased.

The dose should be adjusted according to the individual patient's metabolic response (blood glucose levels and/or glycosylated haemoglobin HbA_{1C}).

Initial dose

The initial recommended dose is 30 mg (half a tablet) once daily, taken with breakfast.

Dose adjustment

If fasting blood glucose levels have not decreased satisfactorily, the dosage can be increased progressively to 60, 90 or 120 mg per day, by successive increments, respecting an interval of at least one month between each increment, except in patients whose blood glucose levels have not decreased after 15 days of treatment.

In this case, it is possible to propose a dosage increase at the end of the second week of treatment.

The daily dose should not exceed 120 mg. Previously untreated patients should commence with a dose of 30 mg.

One **Tendiap MR 60 mg** modified release tablet is equivalent to two **Diaglucide MR 30 mg** modified release tablets.

The breakability of the **Tendiap MR 60 mg** modified release tablet allows the use of a dose of 30 mg as a half tablet and of 90 mg as one and a half tablets.

Replacement of gliclazide 80 mg with Tendiap MR 60 mg

In patients stabilised on gliclazide 80 mg, the replacement of gliclazide 80 mg by **Tendiap MR 60 mg** may initially be based on: 1 tablet gliclazide 80 mg = half a tablet of **Tendiap MR 60 mg.**

Replacement of another sulphonylurea with Tendiap MR 60 mg:

Tendiap MR 60 mg can replace other sulphonylurea treatment. For the transition to **Tendiap MR 60 mg**, the dosage and the half-life of the previous oral hypoglycaemic agent must be taken into account. If a patient is changed from another oral sulphonylurea with a prolonged half-life, a therapeutic window of a few days may prove to be necessary to avoid the additive effect of the two products and the subsequent risk of hypoglycaemia.

During such a changeover, it is recommended to follow the same procedure as for the initiation of the treatment with **Tendiap MR 60 mg**, i.e. to initiate treatment with a dose of 30 mg (half a tablet) per day and then increase the dosage by increments, according to the metabolic evolution of each patient.

Association with other oral antidiabetic agents:

Tendiap MR 60 mg, can be given in combination with alpha glucosidase inhibitors or insulin, but in that case, diabetic control should be checked with blood sugar readings, because of the possibility of hypoglycaemia. In combined therapy with biguanides, there may be a greater risk of cardiovascular mortality than with the use of gliclazide alone.

Special populations:

Elderly patients and patients with renal failure:

The efficacy and tolerance of **Tendiap MR 60 mg**, prescribed using the same therapeutic regimen in subjects over 65 years and patients with mild to moderate renal failure (30 – 80 ml/min) has been confirmed in clinical trials. The dosage will therefore be identical to that recommended for adults under the age of 65 years, and for patients with normal renal function, with careful patient monitoring.

Patient at risk of hypoglycaemia (see section 4.4) It is recommended that the minimum daily starting dose of 30 mg is used.

4.3 Contraindications

Tendiap MR 60 mg is contraindicated in the following cases:

- Hypersensitivity to gliclazide, other sulphonylureas, sulphonamides, or to any of the excipients of **Tendiap MR 60 mg** listed in section 6.1
- Type 1 diabetes (Juvenile Insulin Dependent Diabetes Mellitus)
- Diabetic keto-acidosis, and diabetic pre-coma and coma
- Children
- Severe renal or hepatic insufficiency, in these cases the use of insulin is recommended
- Treatment with miconazole (see section 4.5)
- Pregnancy
- Lactation (see section 4.6).

4.4 Special warnings and precautions for use

Hypoglycaemia:

This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.

Hypoglycaemia may occur following administration of sulphonylureas including **Tendiap MR 60 mg** (see section 4.8). Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days.

Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

The administration of oral hypoglycaemics such as **Tendiap MR 60 mg** may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin.

At risk patients and/or factors favouring hypoglycaemia include (see section 4.2):

- Patients refusing or (particularly elderly patients) being unable to co-operate

- Patients who are malnourished or undernourished, with irregular mealtimes, skipping meals, periods of fasting or dietary changes
- Imbalance between physical exercise and carbohydrate intake
- Certain endocrine disorders: thyroid disorders, hypopituitarism and adrenocorticotrophic insufficiency. These disorders should be controlled by appropriate therapy before introducing **Tendiap MR 60 mg**.
- Withdrawal of prolonged and/or high dose corticosteroid therapy
- Severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease)
- Severe hepatic insufficiency
- Renal insufficiency
- Concomitant administration of certain other medicines (see section 4.5)
- Overdose of **Tendiap MR 60 mg**.

It is recommended that the minimum daily starting dose of 30 mg is used. In an exceptional stress situation e.g. trauma, fever, infection or surgical intervention, St. John's Wort (*Hypericum perforatum*), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.

Gastro-intestinal side effects can be avoided or minimised if **Tendiap MR 60 mg** is taken with breakfast.

Hepato-biliary symptoms usually disappear after discontinuation of treatment. Discontinue treatment if cholestatic jaundice appears.

Beta-blockers may decrease the efficacy of **Tendiap MR 60 mg** (a sulphonylurea) by impairing the release of insulin. Beta-blockers may mask the typical sympathomimetic warning signs and symptoms of hypoglycaemia and may inhibit the normal physiological response to hypoglycaemia.

Patient information:

The risks of hypoglycaemia, together with its symptoms (see section 4.8), treatment, and conditions that predispose to its development, should be explained to the patient and to family members.

The patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

Poor blood glucose control:

Blood glucose control in a patient receiving antidiabetic treatment may be affected by any of the following: fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycaemic efficacy of any oral antidiabetic agent, including gliclazide, is attenuated over time in many patients: this may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure which is distinct

from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

Dysglycaemia:

Disturbances in blood glucose, including hypoglycaemia and hyperglycaemia have been reported, in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in

elderly patients. Careful monitoring of blood glucose is recommended in all patients receiving **Tendiap MR 60 mg** and a fluoroquinolone together.

Laboratory tests:

Measurement of glycosylated haemoglobin levels (or fasting venous plasma glucose) is recommended in assessing blood glucose control. Blood glucose self-monitoring may also be useful.

Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to haemolytic anaemia.

Since gliclazide belongs to the chemical class of sulfonylurea medicines, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Porphyria patients

Cases of acute porphyria have been described with some other sulphonylurea medicines, in patients who have porphyria.

Excipients:

Lactose:

Tendiap MR 60 mg tablets contain lactose.

Patients with rare hereditary problems of galactose intolerance e.g. galactasaemia, Lapp lactase deficiency, or glucose-galactose malabsorption or fructose intolerance should not take **Tendiap MR 60 mg**.

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interactions with other medicinal products and other forms of interaction

The following products are likely to increase the risk of hypoglycaemia:

Contraindicated combination:

- **Miconazole**, (systemic route, oromucosal gel): increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma (see section 4.3).

Combinations which are not recommended:

- **Phenylbutazone** (systemic route): increases the hypoglycaemic effect of sulphonylureas.
- **Alcohol:** increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma. Avoid alcohol or medication containing alcohol.

Combinations requiring precautions for use:

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following medications is taken:

- Other antidiabetic agents (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists)
- Beta-blockers (see section 4.4)
- Fluconazole, ketoconazole (systemic route, oral gel)
- Angiotensin converting enzyme inhibitors (ACE-inhibitors) (captopril, enalapril)
- H2-receptor antagonists (cimetidine, ranitidine)
- Mono-amine-oxidase inhibitors (MAOIs)
- Sulphonamides
- Clarithromycin

- Non-steroidal anti-inflammatory agents (NSAIDS) (including salicylates)
- Chloramphenicol.

The following products may cause an increase in blood glucose levels:

Combination which is not recommended:

- **Danazol**: diabetogenic effect of danazol.

  If the use of this medicine cannot be avoided, warn the patient and emphasise the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

Combinations requiring precautions during use:

- **Chlorpromazine** (neuroleptic agent): high doses (> 100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release).

  Warn the patient and emphasise the importance of blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the neuroleptic agent.
- **Glucocorticoids** (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: increase in blood glucose levels with possible ketosis (reduced tolerance to carbohydrates due to glucocorticoids). Warn the patient and emphasise the importance of

  blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the neuroleptic agent.
- **Salbutamol, terbutaline**: (I.V.) and other beta-adrenergic agonists:

  Increased blood glucose levels due to beta-2 agonist effects.

  Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.
- **Ephedrine, pseudoephedrine and common cold products.**
- **Saint John's Wort (*Hypericum perforatum*) preparations:**

  Gliclazide exposure is decreased by Saint John's Wort (*Hypericum perforatum)*. Emphasise the importance of blood glucose levels monitoring.

The following products may cause dysglycaemia:

Combinations requiring precautions during use:

- **Fluoroquinolones:** in case of concomitant use of **Tendiap MR 60 mg** and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasised.

Combination which must be taken into account:

- **Anticoagulant therapy (warfarin**): sulphonylureas such as **Tendiap MR 60 mg** may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the dose of the anticoagulant may be necessary and INR should be monitored.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established. (see section 4.3).

Pregnancy

There is no or limited amount of data (less than 300 pregnancy outcomes) from the use of gliclazide in pregnant women, even though there are few data with other sulfonylurea.

In animal studies, gliclazide is not teratogenic.

As a precautionary measure, it is preferable to avoid the use of gliclazide during pregnancy.

Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

Oral hypoglycaemic agents are not suitable, insulin is the drug of first choice for treatment of diabetes during pregnancy. It is recommended that oral hypoglycaemic therapy is changed to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered.

Breastfeeding

It is unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, the product is therefore contraindicated in a breastfeeding mother. A risk to the newborns/infants cannot be excluded.

Fertility

No effect on fertility or reproductive performance was noted in male and female rats.

4.7 Effects on ability to drive and use machines

Tendiap MR 60 mg has no or negligible influence on the ability to drive and use machines. However, patients should be made aware of the symptoms of hypoglycaemia, and should be careful when driving, or operating machinery, especially at the beginning of treatment.

4.8 Undesirable effects

Based on the experience with gliclazide and with other sulphonylureas, the following side effects are mentioned for **Tendiap MR 60 mg**.

The following frequency rating has been used: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (≤ 1/ 10 000), not known (cannot be estimated from available data).

The most frequent adverse reaction with **Tendiap MR 60 mg** is hypoglycaemia.

Tendiap MR 60 mg can cause hypoglycaemia, if mealtimes are irregular and, in particular, if meals are skipped.

Possible symptoms of hypoglycaemia are: headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions,
shallow respiration, bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and lethal outcome.

In addition, signs of adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac dysrhythmia.

Usually, symptoms disappear after intake of carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulfonylurea shows that hypoglycaemia can recur even when measures prove effective initially.

If a hypoglycaemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation is required.

Gastrointestinal disorders

Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea and constipation. If these should occur they can be avoided or minimised if **Tendiap MR 60 mg** is taken with breakfast.

The following undesirable effects have been more rarely reported:

Skin and subcutaneous tissue disorders

Rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes and bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis and autoimmune bullous disorders), and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).

Blood and lymphatic system disorders

Changes in haematology are rare. : Anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.

Hepato-biliary disorders

Raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis.

Discontinue treatment if cholestatic jaundice appears.

Eye disorders

Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

Class attribution effects

As for other sulphonylureas the following adverse events have been observed: cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, allergic vasculitis, hyponatraemia, elevated liver enzyme

levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis, which regressed after withdrawal of the sulfonylurea or led to life-threatening liver failure in isolated cases.

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 to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose An overdose of **Tendiap MR 60 mg** may cause hypoglycaemia which could be severe and prolonged. Moderate symptoms of hypoglycaemia, without any loss of consciousness or neurological signs, must be corrected by carbohydrate intake, dose adjustment and/or modification of diet.

Strict monitoring should be continued until the patient is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders should be treated as a medical emergency, requiring immediate hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of 50 ml of concentrated glucose solution (20 - 30 %). This should be followed by continuous infusion of a more dilute solution (10 %), at a rate necessary to maintain blood glucose levels

above 5,5 mmol/l. Patients should be monitored closely, long enough to be sure that hypoglycaemia will not re-occur, and, depending on the patient's condition, the doctor will decide if further monitoring is necessary.

Dialysis is of no use in these patients due to the strong binding of gliclazide to proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2 Oral Hypoglycaemics.

Gliclazide is a hypoglycaemic sulphonylurea agent, which reduces blood glucose levels by stimulating insulin secretion from the ß-cells of the islets of Langerhans. In addition to this pancreatic action, it has been

demonstrated that gliclazide administration may improve the metabolic utilisation of glucose at a peripheral level.

Pharmacokinetic properties:

Absorption

Plasma levels increase progressively until the sixth hour, resulting in a plateau-shaped curve from the sixth to the twelfth hour after administration. Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption. The relationship between the dose administered and the area under the concentration curve, as a function of time, is linear up to
120 mg.

Distribution

Plasma protein binding is approximately 95 %. A single daily dose (varying from half a tablet – 2 tablets) of **Tendiap MR 60 mg** maintains glucose lowering effects over 24 hours.

Biotransformation

Gliclazide is metabolised in the liver and excreted in the urine; less than 1 % of the unchanged form is found in the urine. No active metabolites have been detected in plasma.

Elimination

The elimination half-life of gliclazide varies between 12 and 20 hours.

Linearity/non-linearity

The relationship between the dose administered ranging up to 120 mg and the area under the concentration time curve is linear.

Special populations

Elderly

No clinically significant modifications in the pharmacokinetic parameters have been observed in elderly patients. A single daily dose (varying from half a tablet – 2 tablets) of **Tendiap MR 60 mg** maintains glucose lowering effects over 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,

Hypromellose,

Maltodextrin,

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 30 °C.

Keep the blister in the carton until required for use.

6.5 Nature and contents of container

Blister packs of clear PVC and Aluminium with 30 tablets in a carton.

Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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1686

REGISTRATION NUMBER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 December 2012

10. DATE OF REVISION OF THE TEXT

1 May 2020