**For the use of a Registered Medical Practitioner or Hospital or a Laboratory only**

# EUREPA MF
# (Repaglinide and Metformin Hydrochloride Tablets)

## COMPOSITION
**EUREPA MF 1**
Repaglinide and Metformin Hydrochloride tablets (lmg+500mg)
Each film coated tablet contains: -
Repaglinide I.P. I mg
Metformin Hydrochloride I.P. 500 mg
Colors: Yellow Oxide of Iron & Titanium Dioxide I.P.

**EUREPA MF 2**
Repaglinide and Metformin Hydrochloride tablets (2mg+500mg)
Each film coated tablet contains: -
Repaglinide I.P. 2 mg
Metformin Hydrochloride I.P. 500 mg
Colours: Red Oxide of Iron & Titanium Dioxide I.P.

## DOSAGE FORM
Uncoated tablets

## INDICATIONS
Repaglinide and Metformin Hydrochloride tablet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a Meglitinide and Metformin Hydrochloride or who have inadequate glycemic control on a Meglitinide alone or Metformin Hydrochloride.

## POSOLOGY AND METHOD OF ADMINISTRATION
**Recommended Dosing**
The dosage of Repaglinide and Metformin Hydrochloride tablet should be individualized on the basis of the patient's current regimen, effectiveness and tolerability. Repaglinide and Metformin Hydrochloride tablet can be administered 2 to 3 times a day up to a maximum daily dose of 10 mg Repaglinide/2500 mg Metformin Hydrochloride. No more than 4 mg Repaglinide/1000 mg Metformin Hydrochloride should be taken per meal. Initiation and maintenance of combination therapy with Repaglinide and Metformin Hydrochloride tablet should be individualized to the patient, and at the discretion of the health care provider. Blood glucose monitoring should be performed to determine the therapeutic response to Repaglinide and Metformin Hydrochloride tablet. Repaglinide and Metformin Hydrochloride tablet doses should usually be taken within 15 minutes prior to the meal but the timing can vary from immediately preceding the meal up to 30 minutes before the meal. Patients who skip a meal should be instructed to skip the Repaglinide and Metformin Hydrochloride tablet dose for that meal.

**Patients Inadequately Controlled with Metformin Hydrochloride Monotherapy**
If therapy with a combination tablet containing Repaglinide and Metformin Hydrochloride is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with Metformin Hydrochloride alone, the recommended starting dose of Repaglinide and Metformin Hydrochloride tablet is 1 mg Repaglinide/500mg Metformin Hydrochloride administered twice daily with meals, with gradual dose escalation (based on glycemic response) to reduce the risk of hypoglycaemia with Repaglinide.

**Patients Inadequately Controlled with Meglitinide Monotherapy**
If therapy with a combination tablet containing repaglinide and metformin Hydrochloride is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with repaglinide alone, the recommended starting dose of the metformin Hydrochloride component of Repaglinide and Metformin Hydrochloride tablet should be 500 mg metformin Hydrochloride twice a day, with gradual dose escalation (based on glycemic response) to reduce gastrointestinal side effects associated with metformin Hydrochloride.

**Patients Currently Using Repaglinide and Metformin Hydrochloride Concomitantly**
For patients switching from repaglinide co-administered with metformin Hydrochloride, Repaglinide and Metformin Hydrochloride tablet can be initiated at the dose of repaglinide and metformin Hydrochloride similar to (but not exceeding) the patient's current doses, then may be titrated to the maximum daily dose as necessary to achieve targeted glycemic control.

## CONTRAINDICATIONS

- Hypersensitivity to Repaglinide, metformin or to any of the excipients.
- Diabetes mellitus type 1, C-peptide negative.
- Diabetic ketoacidosis, with or without coma.
- Concomitant use of gemfibrozil
- 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
- Acute or chronic disease which may cause tissue hypoxia such as:
  cardiac or respiratory failure,
  recent myocardial infarction,
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

## SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Metformin**

**Lactic acidosis:**
Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:
The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately.
Physicians should alert the patients on the risk and on the symptoms of lactic acidosis

**Renal function:**
As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels using the Cockcroft-Gault formula) and/or 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 creatinine clearance levels at the limit of normal and in elderly subjects.
Decreased renal function in elderly subjects 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 an NSAID.

**Administration of iodinated contrast agent:**
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. This may induce metformin accumulation which may expose to increase the risk for lactic acidosis. 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.
Surgery:
Metformin hydrochloride should be discontinued 48 hours before elective surgery with 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.
**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.
• Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).
• The tablet shells may be present in the faeces. Patients should be advised that this is normal.

**Repaglinide**
General
Repaglinide should only be prescribed if poor blood glucose control and symptoms of diabetes persist despite adequate attempts at dieting, exercise and weight reduction.
When a patient stabilised on any oral hypoglycaemic medicinal product is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, it may be necessary to discontinue repaglinide and treat with insulin on a temporary basis.
Hypoglycaemia
Repaglinide, like other insulin secretagogues, is capable of producing hypoglycaemia.
Combination with insulin secretagogues
The blood glucose-lowering effect of oral hypoglycaemic medicinal products decreases in many patients over time. This may be due to progression of the severity of the diabetes or to diminished responsiveness to the medicinal product. This phenomenon is known as secondary failure, to distinguish it from primary failure, where the medicinal product is ineffective in an individual patient when first given. Adjustment of dose and adherence to diet and exercise should be assessed before classifying a patient as a secondary failure.
Repaglinide acts through a distinct binding site with a short action on the β-cells. Use of repaglinide in case of secondary failure to insulin secretagogues has not been investigated in clinical trials.

Trials investigating the combination with other insulin secretagogues have not been performed.
Combination with Neutral Protamine Hagedorn (NPH) insulin or thiazolidinediones
Trials of combination therapy with NPH insulin or thiazolidinediones have been performed. However, the benefit risk profile remains to be established when comparing to other combination therapies.
Combination with metformin
Combination treatment with metformin is associated with an increased risk of hypoglycaemia.
Acute coronary syndrome
The use of repaglinide might be associated with an increased incidence of acute coronary syndrome (e.g. myocardial infarction).
Concomitant use
Repaglinide should be used with caution or be avoided in patients receiving medicinal products which influence repaglinide metabolism. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed

**DRUG-INTERACTION**
**Metformin**
*Concomitant use not recommended:*
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 agents
Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.
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:*
Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.
ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.
Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function

**Repaglinide**
A number of medicinal products are known to influence repaglinide metabolism. Possible interactions should therefore be taken into account by the physician:
*In vitro* data indicate that repaglinide is metabolised predominantly by CYP2C8, but also by CYP3A4. Clinical data in healthy volunteers support CYP2C8 as being the most important enzyme involved in repaglinide metabolism with CYP3A4 playing a minor role, but the relative contribution of CYP3A4 can be increased if CYP2C8 is inhibited. Consequently metabolism, and by that clearance of repaglinide, may be altered by substances which influence these cytochrome P-450 enzymes via inhibition or induction. Special care should be taken when inhibitors of both CYP2C8 and 3A4 are co-administered simultaneously with repaglinide.

Based on *in vitro* data, repaglinide appears to be a substrate for active hepatic uptake (organic anion transporting protein OATP1B1). Substances that inhibit OATP1B1 may likewise have the potential to increase plasma concentrations of repaglinide, as has been shown for ciclosporin.

The following substances may enhance and/or prolong the hypoglycaemic effect of repaglinide: Gemfibrozil, clarithromycin, itraconazole, ketokonazole, trimethoprim, ciclosporin, deferasirox, clopidogrel, other antidiabetic substances, monoamine oxidase inhibitors (MAOI), non-selective beta blocking substances, angiotensin converting enzyme (ACE)-inhibitors, salicylates, NSAIDs, octreotide, alcohol, and anabolic steroids.

Co-administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and repaglinide (a single dose of 0.25 mg) increased the repaglinide AUC 8.1-fold and $C_{max}$ 2.4-fold in healthy volunteers. Half-life was prolonged from 1.3 hr to 3.7 hr, resulting in possibly enhanced and prolonged blood glucose-lowering effect of repaglinide, and plasma repaglinide concentration at 7 hr was increased 28.6-fold by gemfibrozil. The concomitant use of gemfibrozil and repaglinide is contraindicated. Co-administration of trimethoprim (160 mg twice daily), a moderate CYP2C8 inhibitor, and repaglinide (a single dose of 0.25 mg) increased the repaglinide AUC, $C_{max}$ and $t_{½}$ (1.6-fold, 1.4-fold and 1.2-fold respectively) with no statistically significant effects on the blood glucose levels. This lack of pharmacodynamic effect was observed with a sub-therapeutic dose of repaglinide. Since the safety profile of this combination has not been established with dosages higher than 0.25 mg for repaglinide and 320 mg for trimethoprim, the concomitant use of trimethoprim with repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

Rifampicin, a potent inducer of CYP3A4, but also CYP2C8, acts both as an inducer and inhibitor of the metabolism of repaglinide. Seven days pre-treatment with rifampicin (600 mg), followed by co-administration of repaglinide (a single dose of 4 mg) at day seven resulted in a 50% lower AUC (effect of a combined induction and inhibition). When repaglinide was given 24 hours after the last rifampicin dose, an 80% reduction of the repaglinide AUC was observed (effect of induction alone). Concomitant use of rifampicin and repaglinide might therefore induce a need for repaglinide dose adjustment which should be based on carefully monitored blood glucose concentrations at both initiation of rifampicin treatment (acute inhibition), following dosing (mixed inhibition and induction), withdrawal (induction alone) and up to approximately two weeks after withdrawal of rifampicin where the inductive effect of rifampicin is no longer present. It cannot be excluded that other inducers, e.g. phenytoin, carbamazepine, phenobarbital, St John's wort, may have a similar effect.

The effect of ketoconazole, a prototype of potent and competitive inhibitors of CYP3A4, on the pharmacokinetics of repaglinide has been studied in healthy subjects. Co-administration of 200 mg ketoconazole increased the repaglinide (AUC and $C_{max}$) by 1.2-fold with profiles of blood glucose concentrations altered by less than 8% when administered concomitantly (a single dose of 4 mg repaglinide). Co-administration of 100 mg itraconazole, an inhibitor of CYP3A4, has also been studied in healthy volunteers, and increased the AUC by 1.4-fold. No significant effect on the glucose level in healthy volunteers was observed. In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, a potent mechanism-based inhibitor of CYP3A4, slightly increased the repaglinide (AUC) by 1.4-fold and $C_{max}$ by 1.7-fold and increased the mean incremental AUC of serum insulin by 1.5-fold and the maximum concentration by 1.6-fold. The exact mechanism of this interaction is not clear.

In a study conducted in healthy volunteers, the concomitant administration of repaglinide (a single dose of 0.25 mg) and ciclosporin (repeated dose at 100 mg) increased repaglinide AUC and $C_{max}$ about 2.5-fold and 1.8-fold respectively. Since the interaction has not been established with dosages higher than 0.25 mg for repaglinide, the concomitant use of ciclosporin with

repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed.
In an interaction study with healthy volunteers, co-administration of deferasirox (30 mg/kg/day, 4 days), a moderate inhibitor of CYP2C8 and CYP3A4, and repaglinide (single dose, 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold (90% CI [2.03-2.63]) of control, a 1.6-fold (90% CI [1.42-1.84]) increase in $C_{max}$, and a small, significant decrease in blood glucose values. Since the interaction has not been established with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed.
In an interaction study with healthy volunteers, co-administration of *clopidogrel* (300 mg loading dose), a CYP2C8 inhibitor, increased repaglinide exposure (AUC0–∞) 5.1-fold and continued administration (75 mg daily dose) increased repaglinide exposure (AUC0–∞) 3.9-fold. A small, significant decrease in blood glucose values was observed. Since the safety profile of the co-treatment has not been established in these patients, the concomitant use of clopidogrel and repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

β-blocking medicinal products may mask the symptoms of hypoglycaemia.
Co-administration of cimetidine, nifedipine, oestrogen, or simvastatin with repaglinide, all CYP3A4 substrates, did not significantly alter the pharmacokinetic parameters of repaglinide.
Repaglinide had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline or warfarin at steady state, when administered to healthy volunteers. Dosage adjustment of these compounds when co-administered with repaglinide is therefore not necessary.
The following substances may reduce the hypoglycaemic effect of repaglinide:
Oral contraceptives, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.
When these medications are administered to or withdrawn from a patient receiving repaglinide, the patient should be observed closely for changes in glycaemic control.
When repaglinide is used together with other medicinal products that are mainly secreted by the bile, like repaglinide, any potential interaction should be considered.
Paediatric population
No interaction studies have been performed in children and adolescents.

## FERTILITY, PREGNANCY AND LACTATION

### Metformin

Pregnancy:
Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.
A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fœtal development, parturition or postnatal development.
When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with 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.

Lactation:
Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.
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.

**Repaglinide**
Pregnancy
There are no studies of repaglinide in pregnant women. Repaglinide should be avoided during pregnancy.
Breast-feeding
There are no studies in breast-feeding women. Repaglinide should not be used in breast-feeding women.
Fertility
Data from animal studies investigating effects on embryofetal and offspring development as well as excretion in milk.

**Effects on ability to drive and use machines**
Repaglinide and metformin has no direct influence on the ability to drive and use machines but may cause hypoglycaemia.
Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

**UNDESIRABLE EFFECTS**
**Metformin**
In post-marketing data and in controlled clinical studies, adverse event reporting in patients treated with metformin was similar in nature and severity to that reported in patients treated with metformin immediate release tablets
The following undesirable effects may occur with metformin:
Frequencies are defined as follows: very common:>1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000 and isolated reports.

| | |
|---|---|
| Metabolism and nutrition disorders | |
| very rare: | Decrease of vitamin $B_{12}$ absorption with decrease of serum levels during long-term use of metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia and lactic acidosis. |
| Nervous system disorders | |
| common: | Taste disturbance |
| Gastrointestinal disorders | |

| | |
|---|---|
| very common: | Gastrointestinal disorders such as 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 gastrointestinal tolerability. |
| Hepatobiliary disorders | |
| isolated reports: | Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation. |
| Skin and subcutaneous tissue disorders | |
| very rare: | Skin reactions such as erythema, pruritus, urticaria |

**Repaglinide**

Summary of the safety profile

The most frequently reported adverse reactions are changes in blood glucose levels, i.e. hypoglycaemia. The occurrence of such reactions depends on individual factors, such as dietary habits, dosage, exercise and stress.

Tabulated list of adverse reactions

Based on the experience with repaglinide and with other hypoglycaemic medicinal products the following adverse reactions have been seen: Frequencies are defined as: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

| | | |
|---|---|---|
| Immune system disorders | Allergic reactions* | Very rare |
| Metabolism and nutrition disorders | Hypoglycaemia | Common |
| | Hypoglycaemic coma and hypoglycaemic unconsciousness | Not known |
| Eye disorders | Refraction disorder* | Very rare |
| Cardiac disorders | Cardiovascular disease | Rare |
| Gastrointestinal disorders | Abdominal pain, diarrhoea | Common |
| | Vomiting, constipation | Very rare |
| | Nausea | Not known |
| Hepatobiliary disorders | Abnormal hepatic function, increased liver enzymes* | Very rare |
| Skin and subcutaneous tissue disorders | Hypersensitivity* | Not known |

* see section Description of selected adverse reactions below

Description of selected adverse reactions

*Allergic reactions*

Generalised hypersensitivity reactions (e.g. anaphylactic reaction), or immunological reactions such as vasculitis.

*Refraction disorders*

Changes in blood glucose levels have been known to result in transient visual disturbances, especially at the commencement of treatment. Such disturbances have only been reported in very few cases after initiation of repaglinide treatment. No such cases have led to discontinuation of repaglinide treatment in clinical trials.

*Abnormal hepatic function, increased liver enzymes*
Isolated cases of increased liver enzymes have been reported during treatment with repaglinide. Most cases were mild and transient, and very few patients discontinued treatment due to increased liver enzymes. In very rare cases, severe hepatic dysfunction has been reported.
*Hypersensitivity*
Hypersensitivity reactions of the skin may occur as erythema, itching, rashes and urticaria. There is no reason to suspect cross-allergenicity with sulphonylurea due to the difference in chemical structure.

**Overdose**
**Metformin**
Hypoglycaemia has not been seen with metformin doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

**Repaglinide**
Repaglinide has been given with weekly escalating doses from 4 - 20 mg four times daily in a 6-week period. No safety concerns were raised. As hypoglycaemia in this study was avoided through increased calorie intake, a relative overdose may result in an exaggerated glucose-lowering effect with development of hypoglycaemic symptoms (dizziness, sweating, tremor, headache etc.). Should these symptoms occur, adequate action should be taken to correct the low blood glucose (oral carbohydrates). More severe hypoglycaemia with seizure, loss of consciousness or coma should be treated with intravenous glucose.

## PHARMACOLOGICAL PROPERTIES

### Metformin

#### Pharmacodynamic properties
ORAL ANTI-DIABETICS
(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.
Metformin may act via 3 mechanisms:
(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
(3) 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).
In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss.
In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

*Clinical efficacy:*
The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetic patients treated with immediate release metformin as first-line therapy after diet failure. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:
• a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/ 1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/ 1000 patient-years), p=0.0034.
• a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/ 1000 patient-years, p=0.017;
• a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1000 patient-years versus diet alone 20.6 events/ 1000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/ 1000 patient-years (p=0.021);
• a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years (p=0.01)
For metformin used as second-line therapy, in combination with a sulphonylurea, 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.

**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 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets bid.
Intrasubject 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).
Metformin absorption from the prolonged release formulation is not altered by meal composition.
No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

**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 63-276 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.

**Repaglinide**

**Pharmacodynamic properties**

Pharmaco-therapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins, ATC code: A10BX02
Mechanism of action
Repaglinide is a short-acting oral secretagogue. Repaglinide lowers the blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β-cells in the pancreatic islets.
Repaglinide closes ATP-dependent potassium channels in the β-cell membrane via a target protein different from other secretagogues. This depolarises the β-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the β-cell.
Pharmacodynamic effects
In type 2 diabetic patients, the insulinotropic response to a meal occurred within 30 minutes after an oral dose of repaglinide. This resulted in a blood glucose-lowering effect throughout the meal period. The elevated insulin levels did not persist beyond the time of the meal challenge. Plasma repaglinide levels decreased rapidly, and low concentrations were seen in the plasma of type 2 diabetic patients 4 hours post-administration.
Clinical efficacy and safety
A dose-dependent decrease in blood glucose was demonstrated in type 2 diabetic patients when administered in doses from 0.5 to 4 mg repaglinide.
Clinical study results have shown that repaglinide is optimally dosed in relation to main meals (preprandial dosing).
Doses are usually taken within 15 minutes of the meal, but the time may vary from immediately preceding the meal to as long as 30 minutes before the meal.
One epidemiological study suggested an increased risk of acute coronary syndrome in repaglinide treated patients as compared to sulfonylurea treated patients.

**Pharmacokinetic properties**
Absorption
Repaglinide is rapidly absorbed from the gastrointestinal tract, which leads to a rapid increase in the plasma concentration of the active substance. The peak plasma level occurs within one-hour post administration. After reaching a maximum, the plasma level decreases rapidly.
Repaglinide pharmacokinetics are characterised by a mean absolute bioavailability of 63% (CV 11%).
No clinically relevant differences were seen in the pharmacokinetics of repaglinide, when repaglinide was administered 0, 15 or 30 minutes before a meal or in fasting state.
A high interindividual variability (60%) in repaglinide plasma concentrations has been detected in the clinical trials. Intraindividual variability is low to moderate (35%) and as repaglinide should be titrated against the clinical response, efficacy is not affected by interindividual variability.

Distribution
Repaglinide pharmacokinetics are characterised by low volume of distribution, 30 L (consistent with distribution into intracellular fluid) and is highly bound to plasma proteins in humans (greater than 98%).

Elimination
Repaglinide is eliminated rapidly within 4 - 6 hours from the blood. The plasma elimination half-life is approximately one hour.
Repaglinide is almost completely metabolised, and no metabolites with clinically relevant hypoglycaemic effect have been identified.
Repaglinide metabolites are excreted primarily via the bile. A small fraction (less than 8%) of the administered dose appears in the urine, primarily as metabolites. Less than 1% of repaglinide is recovered in faeces.

Special patient groups
Repaglinide exposure is increased in patients with hepatic insufficiency and in the elderly type 2 diabetic patients. The AUC (SD) after 2 mg single dose exposure (4 mg in patients with hepatic insufficiency) was 31.4 ng/ml x hr (28.3) in healthy volunteers, 304.9 ng/ml x hr (228.0) in patients with hepatic insufficiency, and 117.9 ng/ml x hr (83.8) in the elderly type 2 diabetic patients.
After a 5-day treatment of repaglinide (2 mg x 3/day) in patients with a severe impaired renal function (creatinine clearance: 20-39 ml/min.), the results showed a significant 2-fold increase of the exposure (AUC) and half-life ($t_{1/2}$) as compared to patients with normal renal function.
*Paediatric population*
No data are available.

## PRECLINICAL SAFETY DATA
**Metformin**
Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

**Repaglinide**
Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Repaglinide was shown not to be teratogenic in animal studies. Embryotoxicity, abnormal limb development in rat foetuses and new born pups, was observed in female rats exposed to high doses in the last stage of pregnancy and during the lactation period. Repaglinide was detected in the milk of animals.

## EXPIRY DATE
Do not use later than the date of expiry.

## PACKAGING INFORMATION
EUREPA MF 1 & EUREPA MF 2 are available in strip of 10 tablets.

## STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not exceeding 30°C. Keep out of reach of children.

**MARKETED BY**


TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

**IN/EUREPA MF 1,2,500mg/AUG-16/03/PI**