SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Repaglinide Krka 2 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg repaglinide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

The tablets are pink, marbled, round, biconvex with bevelled edges and possible darker spots.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Repaglinide is indicated in adults with type 2 diabetes mellitus whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in adults with type 2 diabetes mellitus who are not satisfactorily controlled on metformin alone.

Treatment should be initiated as an adjunct to diet and exercise to lower the blood glucose in relation to meals.

4.2 Posology and method of administration

Posology

Repaglinide is given preprandially and is titrated individually to optimise glycaemic control. In addition to the usual self-monitoring by the patient of blood and/or urinary glucose, the patient's blood glucose must be monitored periodically by the physician to determine the minimum effective dose for the patient. Glycosylated haemoglobin levels are also of value in monitoring the patient's response to therapy. Periodic monitoring is necessary to detect inadequate lowering of blood glucose at the recommended maximum dose level (i.e. primary failure) and to detect loss of adequate blood-glucose-lowering response after an initial period of effectiveness (i.e. secondary failure).

Short-term administration of repaglinide may be sufficient during periods of transient loss of control in Type 2 diabetic patients usually controlled well on diet.

Initial dose

The dosage should be determined by the physician, according to the patient's requirements.

The recommended starting dose is 0.5 mg. One to two weeks should elapse between titration steps (as determined by blood glucose response).

If patients are transferred from another oral hypoglycaemic medicinal product, the recommended starting dose is 1 mg.

Maintenance

The recommended maximum single dose is 4 mg taken with main meals.

The total maximum daily dose should not exceed 16 mg.

Special populations

Elderly

No clinical studies have been conducted in patients >75 years of age.

Renal impairment

Repaglinide is not affected by renal disorders (see section 5.2).

Eight percent of one dose of repaglinide is excreted through the kidneys and total plasma clearance of the product is decreased in patients with renal impairment. As insulin sensitivity is increased in diabetic patients with renal impairment, caution is advised when titrating these patients.

Hepatic impairment

No clinical studies have been conducted in patients with hepatic insufficiency.

Debilitated or malnourished patients

In debilitated or malnourished patients the initial and maintenance dosage should be conservative and careful dose titration is required to avoid hypoglycaemic reactions.

Patients receiving other oral hypoglycaemic medicinal products

Patients can be transferred directly from other oral hypoglycaemic medicinal products to repaglinide. However, no exact dosage relationship exists between repaglinide and the other oral hypoglycaemic medicinal products. The recommended maximum starting dose of patients transferred to repaglinide is 1 mg given before main meals.

Repaglinide can be given in combination with metformin, when the blood glucose is insufficiently controlled with metformin alone. In this case, the dosage of metformin should be maintained and repaglinide administered concomitantly. The starting dose of repaglinide is 0.5 mg, taken before main meals; titration is according to blood glucose response as for monotherapy.

Paediatric population

The safety and efficacy of repaglinide in children below 18 years have not been established. No data are available.

Method of administration

Repaglinide should be taken before main meals (i.e. preprandially).

Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal (i.e. preprandially 2, 3, or 4 meals a day). Patients who skip a meal (or add an extra

meal) should be instructed to skip (or add) a dose for that meal.

In the case of concomitant use with other active substances refer to sections 4.4 and 4.5 to assess the dosage.

4.3 Contraindications

- Hypersensitivity to repaglinide or to any of the excipients listed in section 6.1.
- Diabetes mellitus type 1, C-peptide negative.
- Diabetic ketoacidosis, with or without coma.
- Severe hepatic function disorder.
- Concomitant use of gemfibrozil (see section 4.5).

4.4 Special warnings and precautions for use

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), see sections 4.8 and 5.1.

Concomitant use

Repaglinide should be used with caution or be avoided in patients receiving medicinal products which influence repaglinide metabolism (see section 4.5). If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see below).

The following substances may enhance and/or prolong the hypoglycaemic effect of repaglinide: Gemfibrozil, clarithromycin, itraconazole, ketoconazole, 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 (see section 4.3).

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 (see section 4.4).

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 (see section 4.4).

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 (see section 4.4).

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.

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.

<u>Paediatric population</u>

No interaction studies have been performed in children and adolescents.

4.6 Fertility, pregnancy and lactation

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 is described in section 5.3.

4.7 Effects on ability to drive and use machines

Repaglinide Krka has no or negligible 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.

4.8 Undesirable effects

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)
- 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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.).

Management

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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 (see sections 4.4 and 4.8).

5.2 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.

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)

Calcium hydrogen phosphate

Croscarmellose sodium

Povidone K25

Glycerol

Magnesium stearate

Meglumine

Poloxamer

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister pack (OPA/Alu/PVC-Alu): 30, 60, 90, 120, 270 and 360 tablets in the box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 01656/0342

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

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