Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Repaglinide Arrow 2mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2mg of repaglinide

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Pink round convex tablets with 'R2' on one side and '>' on the other side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Repaglinide is indicated in patients with type 2 diabetes (Non Insulin-Dependent Diabetes Mellitus (NIDDM)) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in type 2 diabetes patients 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

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.

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.

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 agent 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.

Specific patient groups
Repaglinide is primarily excreted via the bile and excretion is therefore not affected by renal disorders. 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.

No clinical studies have been conducted in patients > 75 years of age or in patients with hepatic insufficiency (see section 4.4).

Repaglinide is not recommended for use in children below age 18 due to a lack of data on safety and/or efficacy.

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 agents (OHAs)
Patients can be transferred directly from other oral hypoglycaemic agents to repaglinide. However, no exact dosage relationship exists between repaglinide and the other oral hypoglycaemic agents. 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.

4.3 Contraindications

- Hypersensitivity to repaglinide or to any of the excipients in Repaglinide Arrow
- Type 1 diabetes (Insulin-Dependent Diabetes Mellitus: IDDM), 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.

Repaglinide like other insulin secretagogues, is capable of producing hypoglycaemia.

The blood glucose-lowering effect of oral hypoglycaemic agents decreases in many patients over time. This may be due to progression of the severity of the diabetes or to diminished responsiveness to the product. This phenomenon is known as secondary failure, to distinguish it from primary failure, where the drug 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 and acarbose have not been performed.

Trials of combination therapy with Neutral Protamine Hagedorn (NPH) insulin or thiazolidinediones have been performed. However, the benefit risk profile remains to be established when comparing to other combination therapies.

Combination treatment with metformin is associated with an increased risk of hypoglycaemia.

When a patient stabilised on any oral hypoglycaemic agent 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.

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 drugs 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.

Specific patient groups
No clinical studies have been conducted in patients with impaired hepatic function. No clinical studies have been performed in children and adolescents < 18 years of age or in patients > 75 years of age. Therefore, treatment is not recommended in these patient groups.
Careful dose titration is recommended in debilitated or malnourished patients. The initial and maintenance dosages should be conservative (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

A number of drugs 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 drugs which influence these cytochrome P-450 enzymes via inhibition or induction. Special care should be taken when both inhibitors of CYP2C8 and 3A4 are coadministered simultaneously with repaglinide.

Based on in vitro data, repaglinide appears to be a substrate for active hepatic uptake (organic anion transporting protein OATP1B1). Drugs 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, ketokonazole, trimethoprim, ciclosporin, other antidiabetic agents, monoamine oxidase inhibitors (MAOI), non selective beta blocking agents, 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, Cmax and t½ (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 can not 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 Cmax) 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 Cmax 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 Cmax 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).

β-blocking agents 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 drugs that are mainly secreted by the bile, like repaglinide, any potential interaction should be considered.

4.6 Fertility, pregnancy and lactation

There are no studies of repaglinide in pregnant or lactating women. Therefore the safety of repaglinide in pregnant women cannot be assessed. Up to now repaglinide showed not to be teratogenic in animal studies. Embryotoxicity, abnormal limb development in foetuses and new born pups, was observed in rats exposed to high doses in the last stage of pregnancy and during the lactation period. Repaglinide is detected in the milk of experimental animals. For that reason repaglinide should be avoided during pregnancy and should not be used in lactating women.

4.7 Effects on ability to drive and use machines

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

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

Immune system disorders
Very rare: Allergy
Generalised hypersensitivity reactions (e.g. anaphylactic reaction) or immunological reactions such as vasculitis.

Metabolism and nutrition disorders
Common: Hypoglycaemia
Not known: Hypoglycaemic coma and hypoglycaemic unconsciousness

As with other hypoglycaemic agents, hypoglycaemic reactions have been observed after administration of repaglinide. These reactions are mostly mild and easily handled through intake of carbohydrates. If severe, requiring third party assistance, infusion of glucose may be necessary. The occurrence of such reactions depends, as for every diabetes therapy, on individual factors, such as dietary habits, dosage, exercise and stress (see section 4.4). Interactions with other medicinal products may increase the risk of hypoglycaemia (see section 4.5). During post marketing experience, cases of hypoglycaemia have been reported in patients treated with repaglinide in combination with metformin or thiazolidinedione.

Gastro-intestinal disorders
Common: Abdominal pain and diarrhoea
Very rare: Vomiting and constipation
Not known: Nausea

Gastro-intestinal complaints such as abdominal pain, diarrhoea, nausea, vomiting and constipation have been reported in clinical trials. The rate and severity of these symptoms did not differ from that seen with other oral insulin secretagogues.

Skin and subcutaneous tissue disorders
Not known: Hypersensitivity

Hypersensitivity reactions of the skin may occur as erythema**,** itching, rashes and urticaria. There is no reason to suspect cross-allergenicity with sulphonylurea drugs due to the difference of the chemical structure.

Eye disorders
Very rare: Visual disturbances

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.

Cardiac disorders
Rare: Cardiovascular disease

Type 2 diabetes is associated with an increased risk for cardiovascular disease. In one epidemiological study, a higher incidence of acute coronary syndrome was reported in the repaglinide group. However, the causality of the relationship remains uncertain (see sections 4.4 and 5.1).

Hepato-biliary disorders
Very rare: Hepatic function abnormal
In very rare cases, severe hepatic dysfunction has been reported. However, a causal relationship with repaglinide has not been established.

Very rare: Increased liver enzymes
Isolated cases of increase in liver enzymes have been reported during treatment with repaglinide. Most cases were mild and transient, and very few patients discontinued treatment due to increase in liver enzymes.

4.9 Overdose

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 IV glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Carbamoylmethyl benzoic acid derivative, ATC code: A10B X02

Repaglinide is a novel 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.

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 drug concentrations were seen in the plasma of type 2 diabetic patients 4 hours post-administration. 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

Repaglinide is rapidly absorbed from the gastrointestinal tract, which leads to a rapid increase in the plasma concentration of the drug. The peak plasma level occurs within one hour post administration.

After reaching a maximum, the plasma level decreases rapidly, and repaglinide is eliminated within 4 - 6 hours. The plasma elimination half-life is approximately one hour.

Repaglinide pharmacokinetics are characterised by a mean absolute bioavailability of 63% (CV 11%), low volume of distribution, 30 L (consistent with distribution into intracellular fluid), and rapid elimination from the blood.

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.

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 (t1/2) as compared to subjects with normal renal function.

Repaglinide is highly bound to plasma proteins in humans (greater than 98%).

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.

Repaglinide is almost completely metabolised, and no metabolites with clinically relevant hypoglycaemic effect have been identified. Repaglinide and its 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 the parent drug is recovered in faeces.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Calcium hydrogen phosphate anhydrous
Maize starch
Croscarmellose sodium
Glycerol
Magnesium stearate
Meglumine
Poloxamer
Povidone
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package to protect from light.

6.5 Nature and contents of container

The blister pack (aluminium/aluminium) contains 30, 90, 100, 120, 270 or 360 tablets, respectively. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Arrow ApS
Sankt Peders Straede 2, 1
4000 Roskilde
Denmark

8 MARKETING AUTHORISATION NUMBER

PA 1522/2/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th September 2009

10 DATE OF REVISION OF THE TEXT

November 2011