Public Assessment Report

Decentralised Procedure

MELDIPAN 0.5MG TABLETS
MELDIPAN 1.0MG TABLETS
MELDIPAN 2.0MG TABLETS

Procedure No: UK/H/2157/001-3/DC

UK Licence No: PL 17277/0054-0056

Pharmathen SA
LAY SUMMARY

On 10th February 2010, the MHRA granted Pharmathen SA Marketing Authorisations (licences) for the medicinal products Meldipan 0.5, 1.0 and 2.0mg Tablets (PL 17277/0054-0056). These are prescription-only medicines (POM) that are used to control type 2 diabetes as an add-on to diet and exercise.

The active ingredient repaglinide is an oral antidiabetic agent, which helps your pancreas produce more insulin and thereby lower your blood sugar (glucose).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Meldipan 0.5, 1.0 and 2.0mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

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<td><strong>MA Holder</strong></td>
<td>Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece</td>
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<td><strong>Reference Member State (RMS)</strong></td>
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<tr>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Meldipan 0.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 0.5 mg of repaglinide.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablet

Meldipan 0.5 mg tablets are white, round and biconvex.

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 Meldipan
- 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, ketoconazole, 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.

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).

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, 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 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 coadministration 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.

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 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 to ≤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 in 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: Other blood glucose lowering drugs, excl. insulins, 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 $\beta$-cells in the pancreatic islets.

Repaglinide closes ATP-dependent potassium channels in the $\beta$-cell membrane via a target protein different from other secretagogues. This depolarises the $\beta$-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the $\beta$-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 (E460)
Calcium hydrogen phosphate anhydrous
Maize starch
Amberlite (polacrilin potassium)
6.1 **Active substance:**
Pridoxine 50 mg

**Excipients:**
Povidone
Poloxamer 407
Meglumine
Glycerol
Silica, colloidal anhydrous
Magnesium stearate

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2.5 years

6.4 **Special precautions for storage**
This product does not need any special storage conditions

6.5 **Nature and contents of container**
Meldipan 0.5 mg tablets are packed in PA/ALL/PVC – Aluminium foil blisters with 90 tablets per box.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece
tel.: +30 210 666 4300
fax: +30 210 666 6749
e-mail: info@pharmathen.com

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 17277/0054

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/02/2010

10 **DATE OF REVISION OF THE TEXT**
10/02/2010
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Meldipan 1.0 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1.0 mg of repaglinide.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablet

Meldipan 1.0 mg tablets are yellow, round and biconvex.

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 Meldipan
- 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, ketoconazole, trimethoprim, ciclosporin other anti-diabetic agents, monoamine oxidase inhibitors (MAOI), non selective beta blocking agents, angiotensin converting enzyme (ACE)-inhibitors, salicylates, NSAIDs, octreotide, alcohol and anabolic steroids.

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).

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 Cmax 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, acts both as an inducer and inhibitor of the metabolism of repaglinide. Seven days pre-treatment with rifampicin (600 mg), followed by coadministration 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.

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 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 to ≤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 in 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
- Very rare: Increased liver enzymes

In very rare cases, severe hepatic dysfunction has been reported. However, a causal relationship with repaglinide has not been established.

**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**

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

<table>
<thead>
<tr>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline cellulose (E460)</td>
</tr>
<tr>
<td>Calcium hydrogen phosphate anhydrous</td>
</tr>
<tr>
<td>Maize starch</td>
</tr>
<tr>
<td>Amberlite (polacrilin potassium)</td>
</tr>
<tr>
<td>Povidone</td>
</tr>
<tr>
<td>Poloxamer 407</td>
</tr>
<tr>
<td>Meglumine</td>
</tr>
<tr>
<td>Glycerol</td>
</tr>
<tr>
<td>Silica, colloidal anhydrous</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>Iron oxide yellow (E172)</td>
</tr>
</tbody>
</table>
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2.5 years

6.4 Special precautions for storage
This product does not need any special storage conditions

6.5 Nature and contents of container
Meldipan 1.0 mg tablets are packed in PA/ALL/PVC – Aluminium foil blisters with 90 tablets per box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece
tel.: +30 210 666 4300
fax: +30 210 666 6749
e-mail: info@pharmathen.com

8 MARKETING AUTHORISATION NUMBER(S)
PL 17277/0055

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/02/2010

10 DATE OF REVISION OF THE TEXT
10/02/2010
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Meldipan 2.0 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.0 mg of repaglinide.
For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablet
Meldipan 2.0 mg tablets are pink, round and biconvex.

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.

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
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 Meldipan
- 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).

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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, ketoconazole, 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.

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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.

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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.

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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.

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Not known: Hypersensitivity
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Very rare: Visual disturbances
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Rare: Cardiovascular disease
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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
Pharmacotherapeutic group: Other blood glucose lowering drugs, excl. insulins, ATC code: A10BX02

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 (E460)
- Calcium hydrogen phosphate anhydrous
- Maize starch
- Amberlite (polacrilin potassium)
- Povidone
- Poloxamer 407
- Meglumine
Glycerol  
Silica, colloidal anhydrous  
Magnesium stearate  
Iron oxide red (E172)

6.2 Incompatibilities  
Not applicable.

6.3 Shelf life  
2.5 years

6.4 Special precautions for storage  
This product does not need any special storage conditions

6.5 Nature and contents of container  
Meldipan 2.0 mg tablets are packed in PA/ALL/PVC – Aluminium foil blisters with 90 tablets per box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal  
No special requirements.

7 MARKETING AUTHORISATION HOLDER  
Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece  
tel.: +30 210 666 4300  
fax: +30 210 666 6749  
e-mail: info@pharmathen.com

8 MARKETING AUTHORIZATON NUMBER(S)  
PL 17277/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATON  
10/02/2010

10 DATE OF REVISION OF THE TEXT  
10/02/2010
Module 3
Please note that the generic form of the PIL is provided below. The product will be marketed in the UK under the brand name of Meldipan 0.5mg, 1mg and 2mg Tablets.

PACKAGE LEAFLET: INFORMATION FOR THE USER

[Repaglinide]
0.5 mg tablets
1.0 mg tablets
2.0 mg tablets

Repaglinide

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What [Repaglinide] is and what it is used for
2. Before you take [Repaglinide]
3. How to take [Repaglinide]
4. Possible side effects
5. How to store [Repaglinide]
6. Further information

1. WHAT [REPAGLINIDE] IS AND WHAT IT IS USED FOR

[Repaglinide] is an oral antidiabetic agent containing repaglinide which helps your pancreas produce more insulin and thereby lower your blood sugar (glucose).

Type 2 diabetes is a disease in which your pancreas does not make enough insulin to control the sugar or where your body does not respond normally to the insulin it produces (formerly known as Non-Insulin-Dependent Diabetes Mellitus or maturity onset diabetes).

[Repaglinide] is used to control type 2 diabetes as an add-on to diet and exercise treatment is usually started if diet, exercise and weight reduction alone have not been able to control (or lower) your blood sugar. [Repaglinide] can also be given with metformin, another medicine for diabetes.

2. BEFORE YOU USE [REPAGLINIDE]

Do not take [Repaglinide]:
- If you are hypersensitive (allergic) to repaglinide or any of the other components of the medicine
- If you have type 1 diabetes (Insulin-Dependent Diabetes)
- If the acid level in your body is raised (diabetic ketoacidosis)
- If you have a severe liver disease
- If you take gemfibrozil (a medicine used to lower increased fat levels in the blood).
Take special care with [Repaglinide]:

- If you have liver problems, [Repaglinide] is not recommended in patients with moderate liver disease. [Repaglinide] should not be taken if you have a severe liver disease (see Do not take [Repaglinide]).
- If you have kidney problems, [Repaglinide] should be taken with caution.
- If you are about to have major surgery or you have recently suffered a severe illness or infection. At such times diabetic control may be lost.
- If you are under 18 or over 75 years of age, [Repaglinide] is not recommended. It has not been studied in these age groups.

Talk to your doctor if any of the above applies to you. [Repaglinide] may not be suitable for you. Your doctor will advise you.

If you get a hypo

You may get a hypo (short for a hypoglycemic reaction and is symptoms of low blood sugar) if your blood sugar gets too low. This may happen:

- If you take too much [Repaglinide]
- If you exercise more than usual
- If you take other medicines or suffer from liver or kidney problems (see other sections of 2. Before you take [Repaglinide]).

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

If your blood sugar is low or you feel a hypo coming on, eat glucose tablets or a high sugar snack or drink, then rest.

When symptoms of hypoglycemia have disappeared or when blood sugar levels are stabilised continue [Repaglinide] treatment.

Tell people you have diabetes that if you pass out (become unconscious) due to a hypo, they must turn you on your side and get medical help straight away. They must not give you any food or drink. It could choke you.

- If severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death.
- If you have a hypo that makes you pass out, or a lot of hypoes, talk to your doctor. The amount of [Repaglinide], food or exercise may need to be adjusted.

If your blood sugar gets too high

Your blood sugar may get too high (hyperglycaemia). This may happen:

- If you take too little [Repaglinide]
- If you have an illness or a fever
- If you eat more than usual
- If you exercise less than usual.

The warning signs appear gradually. They include increased urination, feeling thirsty, dry skin and dry mouth. Talk to your doctor. The amount of [Repaglinide], food or exercise may need to be adjusted.

Using other medicines

You can take [Repaglinide] with metformin, another medicine for diabetes, if your doctor prescribes it. If you take gemfibrozil (used to lower increased fat levels in the blood) you should not take [Repaglinide].
Your body's response to [Repaglinide] may change if you take other medicines, especially these:

- Monoamine oxidase inhibitors (MAOI) used to treat depression
- Beta blockers (used to treat high blood pressure or heart conditions)
- ACE inhibitors (used to treat heart conditions)
- Salicylates (e.g. aspirin)
- Ocreotide (used to treat cancer)
- Nonsteroidal anti-inflammatory drugs (NSAID) (a type of painkillers)
- Steroids (anabolic steroids and corticosteroids – used for premenia or to treat inflammation)
- Oral contraceptives (birth control pills)
- Thiazides (diuretics or "water pills")
- Danazol (used to treat breast cysts and endometriosis)
- Thyroid products (used to treat low levels of thyroid hormones)
- Sympathomimetics (used to treat asthma)
- Clarithromycin, trimethoprim, rifampicin (antibiotic medicines)
- Itraconazole, ketoconazole (antifungal medicines)
- Gemfibrozil (used to treat high blood fats)
- Ciclosporin (used to suppress the immune system)
- Phenytoin, carbamazepine, phenobarbital (used to treat epilepsy)
- St. John's wort (herbal medicine).

Tell your doctor if you have recently taken or are planning to take any of these medicines, or any medicines obtained without a prescription.

**Using [Repaglinide] with food and drink**

Take [Repaglinide] before main meals. Alcohol can change the ability of [Repaglinide] to reduce the blood sugar. Watch for signs of hypo.

**Pregnancy and breast-feeding**

You should not take [Repaglinide] if you are pregnant or you are planning to become pregnant. See your doctor as soon as possible if you become pregnant or are planning to become pregnant during treatment.

You should not take [Repaglinide] if you are breast-feeding.

**Driving and using machines**

Your ability to drive or operate a machine may be affected if your blood sugar is low or high. Bear in mind that you could endanger yourself or other. Please ask your doctor whether you can drive a car if you:

- Have frequent hypos
- Have few or no warning signs of hypos.

**3. HOW TO TAKE [REPAGLINIDE]**

Your doctor will work out your dose.

- The normal starting dose is 0.5 mg before each main meal. Swallow the tablets with a glass of water immediately before or up to 30 minutes before each main meal.
- The dose may be adjusted by your doctor by up to 4 mg to be taken immediately before or up to 30 minutes before each main meal. The maximum recommended daily dose is 15 mg.
Do not take more [Repaglinide] than your doctor has recommended. Always take [Repaglinide] exactly as your doctor has told you. Check with your doctor if you are not sure.

If you take more [Repaglinide] than you should

If you take too many tablets, your blood sugar may become too low, leading to a hypo. Please see If you get a hypo on what a hypo is and how to treat it.

If you forget to take [Repaglinide]

If you miss a dose, take the next dose as usual - do not double the dose.

If you stop taking [Repaglinide]

Be aware that the desired effect is not achieved if you stop taking [Repaglinide]. Your diabetes may get worse. If any change of your treatment is necessary contact your doctor first.

If you have any further questions on the use of [Repaglinide], ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, [Repaglinide] can cause side effects, although not everybody gets them.

Possible side effects

Common (may affect up to 1 in 10 patients)
- Hypoglycaemia (see If you get a hypo). The risk of getting a hypo may increase if you take other medicines
- Stomach pain
- Diarrhoea

Rare (may affect up to 1 in 1000 patients)
- Acute coronary syndrome (but it may not be due to the drug)

Very rare (may affect up to 1 in 10,000 patients)
- Allergy (such as swelling, difficulty in breathing, rapid heart beat, feeling dizzy, sweating which could be signs of anaphylactic reaction). Contact a doctor immediately
- Vomiting
- Constipation
- Visual disturbances
- Severe liver problems, abnormal liver function, increased liver enzymes in your blood.

Frequency unknown
- Hypoglycaemic coma or unconsciousness (very severe hypoglycaemic reactions – see If you get a hypo). Contact a doctor immediately
- Hypersensitivity (such as rash, itchy skin, reddening of the skin, swelling of the skin)
- Feeling sick (nausea).

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.
5. **HOW TO STORE [REPAGLINIDE]**

Keep out of the reach and sight of children.

*This product does not need any special storage conditions*

Do not use the product after the expiry date. The expiry date refers to the last date of that month. This is stated on the outer carton and the blister foil.

Medicines should not be disposed of down the drain or in household rubbish. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What [Repaglinide] contains**

The active substance is repaglinide.

The other ingredients are:

- Microcrystalline cellulose (E460), calcium hydrogen phosphate anhydrous, maize starch, amberlite (polacrilm potassium), , poloxamer 407, magnesium stearate, iron oxide yellow (E172) only in the 1.0 mg tablets and iron oxide red (E172) only in the 2.0 mg tablets.

Three strengths of tablets are available. The strengths are 0.5 mg, 1.0 mg, and 2.0 mg.

**What [Repaglinide] looks like and contents of the pack**

[Repaglinide] tablets are round and biconvex. 0.5 mg tablets are white, 1.0 mg tablets are yellow and 2.0 mg tablets are pink.

[Repaglinide] are available in blister packs of 30, 90 and 120 tablets. Not all pack sizes may be marketed.

**Marketing authorisation holder and manufacturer**

*Marketing Authorization Holder*

[To be completed nationally]

(Name and address)

(tel)

(fax)

(e-mail)

*Manufacturer*

Pharmathen S.A., Der Varnakion 6, 15351 Pallini, Attiki, Greece
tel.: +30 210 666 4300
fax: +30 210 666 5719
(e-mail: info@pharmathen.com)
Industrial Park Sapes Rodopi Perfecture, Block 5, Rodopi 69300, Greece
tel. +30 23320 31375
fax. +30 23320 31471
e-mail: info@pharmathen.com

This medicinal product is authorised in the Member States of the EEA under the following names:

**UK/H/2992/01-03/DC**
- United Kingdom: Theroflan Strengths: 0.5 mg, 1 mg, 2 mg
- Cyprus: Theroflan Strengths: 0.5 mg, 1 mg, 2 mg
- Greece: Theroflan Strengths: 0.5 mg, 1 mg, 2 mg
- Italy: Theroflan Strengths: 0.5 mg, 1 mg, 2 mg

**UK/H/2157/01-03/DC**
- United Kingdom: Meldipan Strengths: 0.5 mg, 1 mg, 2 mg
- Estonia: Meldipan Strengths: 0.5 mg, 1 mg, 2 mg
- Lithuania: Meldipan Strengths: 0.5 mg, 1 mg, 2 mg
- Latvia: Meldipan Strengths: 0.5 mg, 1 mg, 2 mg
- Iceland: Meldipan Strengths: 0.5 mg, 1 mg, 2 mg
- Italy: Meldipan Strengths: 0.5 mg, 1 mg, 2 mg

This leaflet was last approved in
Module 4
Labelling

Please note that the generic form of the labelling is provided below. The product will be marketed in the UK under the brand name of Meldipan 0.5mg, 1mg and 2mg Tablets.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

[Repaglinide] 0.5 mg tablets

Repaglinide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg Repaglinide

3. LIST OF EXCIPIENTS

Glycerol is one of the excipients

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets
120 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This product does not need any special storage conditions
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHOURISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Repaglinide] 0.5 mg
| MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS |
| Blistter Foil |

| 1. NAME OF THE MEDICINAL PRODUCT |
| [Repaglinide] 0.5 mg tablets |
| Repaglinide |

| 2. NAME OF THE MARKETING AUTHORISATION HOLDER |
| [To be completed nationally] |
| (Name) |

| 3. EXPIRY DATE |
| EXP |

| 4. BATCH NUMBER |
| Lot |

| 5. OTHER |
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

1. **NAME OF THE MEDICINAL PRODUCT**

[Repaglinide] 1.0 mg tablets

Repaglinide

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 1.0 mg Repaglinide

3. **LIST OF EXCIPIENTS**

Glycerol is one of the excipients

4. **PHARMACEUTICAL FORM AND CONTENTS**

<table>
<thead>
<tr>
<th>Quantity</th>
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<tbody>
<tr>
<td>30 tablets</td>
</tr>
<tr>
<td>90 tablets</td>
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<tr>
<td>120 tablets</td>
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</table>

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

This product does not need any special storage conditions.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Repaglinide] 1.0 mg
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**BLISTER FOIL**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>[Repaglinide] 1.0 mg tablets</td>
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<tr>
<td>[To be completed nationally]</td>
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<tr>
<td>[Name]</td>
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<th>3. EXPIRY DATE</th>
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<th>4. BATCH NUMBER</th>
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<td>Lot</td>
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</table>

<table>
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<tr>
<th>5. OTHER</th>
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</thead>
<tbody>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</td>
</tr>
<tr>
<td>OUTER CARTON</td>
</tr>
</tbody>
</table>

| 1. NAME OF THE MEDICINAL PRODUCT |
| [Repaglinide] 2.0 mg tablets: |
| Repaglinide |

| 2. STATEMENT OF ACTIVE SUBSTANCE(S) |
| Each tablet contains 2.0 mg Repaglinide |

| 3. LIST OF EXCIPIENTS |
| Glycerol is one of the excipients |

| 4. PHARMACEUTICAL FORM AND CONTENTS |
| 30 tablets |
| 90 tablets |
| 120 tablets |

| 5. METHOD AND ROUTE(S) OF ADMINISTRATION |
| Read the package leaflet before use. |
| Oral use. |

| 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN |
| Keep out of the reach and sight of children. |

| 7. OTHER SPECIAL WARNING(S), IF NECESSARY |
| 8. EXPIRY DATE |
| EXP |

| 9. SPECIAL STORAGE CONDITIONS |
| This product does not need any special storage conditions |
10. SPECIAL PRECAUTIONS FOR DISPOAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE


16. INFORMATION IN BRAILLE

{Repaglinide} 2.0 mg

[Repaglinide] 2.0 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

[Repaglinide] 2.0 mg tablets

Repaglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Meldipan 0.5, 1.0 and 2.0mg Tablets (PL 17277/0054-0056; UK/H/2157/001-3/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS) and Estonia, Iceland, Italy, Latvia and Lithuania as concerned member states (CMS):

The products are prescription-only medicines 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.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of NovoNorm 0.5, 1.0 and 2.0mg Tablets, which were originally granted licences in 1998 to Novo Nordisk A/S.

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 $\beta$-cells in the pancreatic islets. It 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 1 hour post administration. After reaching a maximum, the plasma level decreases rapidly, and it is eliminated within 4 - 6 hours. The plasma elimination half-life is approximately 1 hour.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 12th January 2010. After a subsequent national phase, the licences were granted in the UK on 10th February 2010.
## ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Meldipan 0.5mg Tablets  
Meldipan 1.0mg Tablets  
Meldipan 2.0mg Tablets |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Repaglinide</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Carbamoylmethyl benzoic acid derivative (A10B X02)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>0.5, 1.0 and 2.0 Tablets</td>
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<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/2157/001-3/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Estonia, Iceland, Italy, Latvia and Lithuania</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 17277/0054-0056</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece</td>
</tr>
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</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Repaglinide

Chemical Name:
INN: Repaglinide

Chemical Name: (S)-2-Ethoxy-4-[3-[methyl-l-[2-[(1-piperidinyl)phenyl]butyl]amino]-2-

oxoethyl]benzoic acid

(S)-(+)2-ethoxy-4-[N-[1-(2-piperidinophenyl)-3-methyl-1-butyl] aminocarbonylmethyl] benzoic acid

Chemical Structure:

Molecular Formula: C_{27}H_{36}N_{2}O_{4}

Molecular Weight: 452.59

Appearance: white or almost white powder practically insoluble in water, freely

soluble in methanol and in methylene chloride.

Synthesis of the drug substance from the designated starting materials has been adequately
described and appropriate in-process controls and intermediate specifications are applied.
Satisfactory specification tests are in place for all starting materials and reagents and these
are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have
been appropriately validated and are satisfactory for ensuring compliance with the relevant
specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical
ingredient. All potential known impurities have been identified and characterised.
Satisfactory certificates of analysis have been provided for all working standards. Batch
analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging
has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored
in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose (E460),
calcium hydrogen phosphate anhydrous, maize starch, amberlite (polacrilin potassium),
povidone, poloxamer 407, meglumine, glycerol, silica colloidal anhydrous, magnesium
stearate. Additionally, the 1.0mg strength tablets contain iron oxide yellow (E172) and the
2.0mg tablets contain iron oxide red (E172).

All excipients comply with their respective European Pharmacopoeia monograph, with the
exception of yellow iron oxide and red iron oxide (which is controlled to a suitable USP
monograph). Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to formulate robust, stable tablets that were containing qualitatively and quantitatively the same as Novonorm Tablets (Novo Nordisk A/S), and exhibiting the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications.

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
All strengths of tablets are packaged in polyvinylchloride/aluminium/polyamide blisters in pack sizes of 90 film-coated tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2.5 years, with no specific storage conditions.

Suitable post approval stability commitments have been provided.

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.
Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable. The PIL and labels provided are in the generic form; it should be noted that the product will be marketed in the UK under the brand name of Meldipan 0.5mg, 1mg and 2mg Tablets.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of repaglinide are well-known, no further preclinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a preclinical viewpoint.
III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Repaglinide 2mg Tablets versus the reference product Novonorm 2mg Tablets (Novo Nordisk A/S) in healthy volunteers under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 12 hours post dose. The two treatment arms were separated by a 7-day washout period.

The log-transformed pharmacokinetic results are presented below:

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<tr>
<th>Parameter</th>
<th>Test ± CV (%)</th>
<th>Reference ± CV (%)</th>
<th>Repaglinide test/reference ratio %, 90% confidence intervals</th>
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<tr>
<td>Cmax (ng/mL)</td>
<td>31.4 ± 38.8</td>
<td>31.8 ± 46.7</td>
<td>101.1, 91.9–111.3</td>
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<tr>
<td>AUCt (ng.h/mL)</td>
<td>43.3 ± 37.5</td>
<td>43.8 ± 46.8</td>
<td>101.5, 97.5–105.5</td>
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<tr>
<td>AUC∞ (ng.h/mL)</td>
<td>44.9 ± 36.7</td>
<td>45.3 ± 46.2</td>
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<tr>
<td>Tmax (h)*</td>
<td>0.7 ± 96.6</td>
<td>0.8 ± 51.6</td>
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The 90% confidence intervals for Cmax and AUC for test vs reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

As the 0.5, 1.0 and 2.0mg strengths of the product meet all the criteria as specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study on the 2.0mg strength to the 0.5mg and 1mg presentations, is justified.

Efficacy

No new data on the efficacy have been submitted and none are required for these types of applications.

Safety

No new or unexpected safety issues were raised by the bioequivalence data.

SPC, PIL, Labels

The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of marketing authorisations is recommended.
IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Meldipan 0.5, 1.0 and 2.0mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s repaglinide 2.0mg Tablets and its respective reference product. As the 0.5, 1.0 and 2.0mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 2.0mg strength can be extrapolated to the 0.5 and 1.0mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with repaglinide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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