Public Assessment Report

Decentralised Procedure

Repaglinide Chanelle Medical 0.5 mg, 1 mg and 2 mg Tablets

repaglinide

UK licence no: PL 13931/0057-9

Chanelle Medical
LAY SUMMARY

On 25th April 2012, the Reference Member State (RMS) and the Concerned Member States (CMSs) agreed to grant Marketing Authorisations to Chanelle Medical for the medicinal products Repaglinide Chanelle Medical 0.5, 1 and 2 mg Tablets. These marketing authorisations were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 23rd May 2012. These medicines are only available on prescription from your doctor.

Repaglinide tablet 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 in your blood 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.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Repaglinide Chanelle Medical 0.5, 1 and 2 mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

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<td>Loughrea, Co. Galway, Ireland</td>
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Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Repaglinide Chanelle Medical 0.5 mg Tablets

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

Excipient(s):
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

0.5 mg: White to off white, round, biconvex tablets debossed with ‘M’ on one side of the tablet and ‘R21’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Repaglinide is indicated in patients with type 2 diabetes (Non Insulin-Dependent Diabetes Mellitus (NIDDM)) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in type 2 diabetes patients who are not satisfactorily controlled on metformin alone.

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

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

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

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

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

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

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

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

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

Maintenance
The recommended maximum single dose is 4 mg taken with main meals. The total maximum daily dose should not exceed 16 mg.
Specific patient groups
Repaglinide is primarily excreted via the bile and excretion is therefore not affected by renal disorders. Eight percent of one dose of repaglinide is excreted through the kidneys and total plasma clearance of the product is decreased in patients with renal impairment. As insulin sensitivity is increased in diabetic patients with renal impairment, caution is advised when titrating these patients.

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

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

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

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

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

4.3 Contraindications
- Hypersensitivity to repaglinide or to any of the excipients in Prandin.
- 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, ciclosporin, clarithromycin, itraconazole, ketoconazole, trimethoprim, other antidiabetic agents, monoamine oxidase inhibitors (MAOI), non selective beta blocking agents, angiotensin converting enzyme (ACE)-inhibitors, salicylates, NSAIDs, octreotide, alcohol, and anabolic steroids.

Co-administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and repaglinide (a single dose of 0.25 mg) increased the repaglinide AUC 8.1-fold and C\text{max} 2.4-fold in healthy volunteers. Half-life was prolonged from 1.3 hr to 3.7 hr, resulting in possibly enhanced and prolonged blood glucose-lowering effect of repaglinide, and plasma repaglinide concentration at 7 hr was increased 28.6-fold by gemfibrozil. The concomitant use of gemfibrozil and repaglinide is contraindicated (see section 4.3).

Co-administration of trimethoprim (160 mg twice daily), a moderate CYP2C8 inhibitor, and repaglinide (a single dose of 0.25 mg) increased the repaglinide AUC, C\text{max} and t\text{1/2} (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 C_{max}) by 1.2-fold with profiles of blood glucose concentrations altered by less than 8% when administered concomitantly (a single dose of 4 mg repaglinide). Co-administration of 100 mg itraconazole, an inhibitor of CYP3A4, has also been studied in healthy volunteers, and increased the AUC by 1.4-fold. No significant effect on the glucose level in healthy volunteers was observed. In an interaction study in healthy volunteers, coadministration of 250 mg clarithromycin, a potent mechanism-based inhibitor of CYP3A4, slightly increased the repaglinide (AUC) by 1.4-fold and C_{max} by 1.7-fold and increased the mean incremental AUC of serum insulin by 1.5-fold and the maximum concentration by 1.6-fold. The exact mechanism of this interaction is not clear.

In a study conducted in healthy volunteers, the concomitant administration of repaglinide (a single dose of 0.25 mg) and ciclosporin (repeated dose at 100 mg) increased repaglinide AUC and C_{max} about 2.5-fold and 1.8-fold respectively. Since the interaction has not been established with dosages higher than 0.25 mg for repaglinide, the concomitant use of ciclosporin with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4).

β-blocking agents may mask the symptoms of hypoglycaemia.

Co-administration of cimetidine, nifedipine, oestrogen, or simvastatin with repaglinide, all CYP3A4 substrates, did not significantly alter the pharmacokinetic parameters of repaglinide.

Repaglinide had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline or warfarin at steady state, when administered to healthy volunteers. Dosage adjustment of these compounds when co-administered with repaglinide is therefore not necessary.

The following substances may reduce the hypoglycaemic effect of repaglinide: Oral contraceptives, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.

When these medications are administered to or withdrawn from a patient receiving repaglinide, the patient should be observed closely for changes in glycaemic control.

When repaglinide is used together with other drugs that are mainly secreted by the bile, like repaglinide, any potential interaction should be considered.

4.6 Fertility pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Based on the experience with repaglinide and with other hypoglycaemic agents the following adverse events have been seen: Frequencies are defined as: Common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 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 of the chemical structure.

**Eye disorders**
Very rare: Visual disturbances.

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

**Cardiac disorders**
Rare: Cardiovascular disease.

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

**Hepato-biliary disorders**
Very rare: Hepatic function abnormal.

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

Very rare: Increased liver enzymes.

Isolated cases of increase in liver enzymes have been reported during treatment with repaglinide. Most cases were mild and transient, and very few patients discontinued treatment due to increase in liver enzymes.
4.9 Overdose
Repaglinide has been given with weekly escalating doses from 4 - 20 mg four times daily in a 6-week period. No safety concerns were raised. As hypoglycaemia in this study was avoided through increased calorie intake, a relative overdose may result in an exaggerated glucose lowering effect with development of hypoglycaemic symptoms (dizziness, sweating, tremor, headache etc.). Should these symptoms occur, adequate action should be taken to correct the low blood glucose (oral carbohydrates). More severe hypoglycaemia with seizure, loss of consciousness or coma should be treated with IV glucose.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmaco-therapeutic group: Carbamoylmethyl benzoic acid derivative, ATC code: A10B X02.

Repaglinide is a novel short-acting oral secretagogue. Repaglinide lowers the blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β-cells in the pancreatic islets.

Repaglinide closes ATP-dependent potassium channels in the β-cell membrane via a target protein different from other secretagogues. This depolarises the β-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the β-cell.

In type 2 diabetic patients, the insulinotropic response to a meal occurred within 30 minutes after an oral dose of repaglinide. This resulted in a blood glucose-lowering effect throughout the meal period. The elevated insulin levels did not persist beyond the time of the meal challenge. Plasma repaglinide levels decreased rapidly, and low drug concentrations were seen in the plasma of type 2 diabetic patients 4 hours post-administration.

A dose-dependent decrease in blood glucose was demonstrated in type 2 diabetic patients when administered in doses from 0.5 to 4 mg repaglinide.

Clinical study results have shown that repaglinide is optimally dosed in relation to main meals (preprandial dosing).

Doses are usually taken within 15 minutes of the meal, but the time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

One epidemiological study suggested an increased risk of acute coronary syndrome in repaglinide treated patients as compared to sulfonylurea treated patients (see sections 4.4 and 4.8).

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

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

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

A high interindividual variability (60%) in repaglinide plasma concentrations has been detected in the clinical trials. Intraindividual variability is low to moderate (35%) and as repaglinide should be titrated against the clinical response, efficacy is not affected by interindividual variability.

Repaglinide exposure is increased in patients with hepatic insufficiency and in the elderly type 2 diabetic patients. The AUC (SD) after 2 mg single dose exposure (4 mg in patients with hepatic insufficiency) was 31.4 ng/ml x hr (28.3) in healthy volunteers, 304.9 ng/ml x hr (228.0) in patients with hepatic insufficiency, and 117.9 ng/ml x hr (83.8) in the elderly type 2 diabetic patients. After a 5 day treatment of repaglinide (2 mg x 3/day) in patients with a severe impaired renal function (creatinine clearance: 20-39 ml/min.), the results showed a significant 2-fold increase of the exposure (AUC) and half-life (t1/2) as compared to subjects with normal renal function.
Repaglinide is highly bound to plasma proteins in humans (greater than 98%).

No clinically relevant differences were seen in the pharmacokinetics of repaglinide, when repaglinide was administered 0, 15 or 30 minutes before a meal or in fasting state.

Repaglinide is almost completely metabolised, and no metabolites with clinically relevant hypoglycaemic effect have been identified.

Repaglinide and its metabolites are excreted primarily via the bile. A small fraction (less than 8%) of the administered dose appears in the urine, primarily as metabolites. Less than 1% of the parent drug is recovered in faeces.

5.3 Preclinical safety data
Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Povidone
Sodium lauril sulfate
Butylhydroxyanisole
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline (E460)
Maize starch
Meglumine
Croscarmellose sodium
Polacrilin potassium
Magnesium stearate
Silica, colloidal anhydrous

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Blisters packs: 2 years
HDPE bottle packs: 2 years. Once opened use within 3 months.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Aluminium/Aluminium blisters in an outer carton (pack sizes of 30, 90, 120, 180, 200 and 270 tablets), or HDPE bottles with PP (Polypropylene) closure and desiccant (containing 120, 200 and 270 tablets). Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Chanelle Medical
Loughrea, Co. Galway, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 13931/0057

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/05/2012

10 DATE OF REVISION OF THE TEXT
23/05/2012
1 NAME OF THE MEDICINAL PRODUCT
Repaglinide Chanelle Medical 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1 mg of repaglinide

Excipient(s):
For a full list of excipients, see section 6.1.

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Tablet

1 mg: Yellow coloured, round, biconvex tablets debossed with ‘M’ on one side of the tablet and ‘R22’ on the other side

4 CLINICAL PARTICULARS
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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.

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

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Specific patient groups
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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.

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

Co-administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and repaglinide (a single dose of 0.25 mg) increased the repaglinide AUC 8.1-fold and 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, 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, coadministration of 250 mg clarithromycin, a potent mechanism-based inhibitor of CYP3A4, slightly increased the repaglinide (AUC) by 1.4-fold and Cmax by 1.7-fold and increased the mean incremental AUC of serum insulin by 1.5-fold and the maximum concentration by 1.6-fold. The exact mechanism of this interaction is not clear.

In a study conducted in healthy volunteers, the concomitant administration of repaglinide (a single dose of 0.25 mg) and ciclosporin (repeated dose at 100 mg) increased repaglinide AUC and Cmax about 2.5-fold and 1.8-fold respectively. Since the interaction has not been established with dosages higher than 0.25 mg for repaglinide, the concomitant use of ciclosporin with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4).

β-blocking agents may mask the symptoms of hypoglycaemia.

Co-administration of cimetidine, nifedipine, oestrogen, or simvastatin with repaglinide, all CYP3A4 substrates, did not significantly alter the pharmacokinetic parameters of repaglinide.

Repaglinide had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline or warfarin at steady state, when administered to healthy volunteers. Dosage adjustment of these compounds when co-administered with repaglinide is therefore not necessary.

The following substances may reduce the hypoglycaemic effect of repaglinide: Oral contraceptives, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.

When these medications are administered to or withdrawn from a patient receiving repaglinide, the patient should be observed closely for changes in glycaemic control.

When repaglinide is used together with other drugs that are mainly secreted by the bile, like repaglinide, any potential interaction should be considered.

4.6 Fertility pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Based on the experience with repaglinide and with other hypoglycaemic agents the following adverse events have been seen: Frequencies are defined as: Common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 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 of the chemical structure.

Eye disorders
Very rare: Visual disturbances.

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

Cardiac disorders
Rare: Cardiovascular disease.

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

Hepato-biliary disorders
Very rare: Hepatic function abnormal.

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

Very rare: Increased liver enzymes.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Repaglinide is a novel short-acting oral secretagogue. Repaglinide lowers the blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β-cells in the pancreatic islets.

Repaglinide closes ATP-dependent potassium channels in the β-cell membrane via a target protein different from other secretagogues. This depolarises the β-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the β-cell.

In type 2 diabetic patients, the insulinotropic response to a meal occurred within 30 minutes after an oral dose of repaglinide. This resulted in a blood glucose-lowering effect throughout the meal period. The elevated insulin levels did not persist beyond the time of the meal challenge. Plasma repaglinide levels decreased rapidly, and low drug concentrations were seen in the plasma of type 2 diabetic patients 4 hours post-administration.

A dose-dependent decrease in blood glucose was demonstrated in type 2 diabetic patients when administered in doses from 0.5 to 4 mg repaglinide.

Clinical study results have shown that repaglinide is optimally dosed in relation to main meals (preprandial dosing).

Doses are usually taken within 15 minutes of the meal, but the time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

One epidemiological study suggested an increased risk of acute coronary syndrome in repaglinide treated patients as compared to sulfonylurea treated patients (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

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

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

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

A high interindividual variability (60%) in repaglinide plasma concentrations has been detected in the clinical trials. Intraindividual variability is low to moderate (35%) and as repaglinide should be titrated against the clinical response, efficacy is not affected by interindividual variability.

Repaglinide exposure is increased in patients with hepatic insufficiency and in the elderly type 2 diabetic patients. The AUC (SD) after 2 mg single dose exposure (4 mg in patients with hepatic insufficiency) was 31.4 ng/ml x hr (28.3) in healthy volunteers, 304.9 ng/ml x hr (228.0) in patients with hepatic insufficiency, and 117.9 ng/ml x hr (83.8) in the elderly type 2 diabetic patients. After a 5 day treatment of repaglinide (2 mg x 3/day) in patients with a severe impaired renal function (creatinine clearance: 20-39 ml/min.), the results showed a significant 2-fold increase of the exposure (AUC) and half-life (t1/2) as compared to subjects with normal renal function.
Repaglinide is highly bound to plasma proteins in humans (greater than 98%).

No clinically relevant differences were seen in the pharmacokinetics of repaglinide, when repaglinide was administered 0, 15 or 30 minutes before a meal or in fasting state.

Repaglinide is almost completely metabolised, and no metabolites with clinically relevant hypoglycaemic effect have been identified.

Repaglinide and its metabolites are excreted primarily via the bile. A small fraction (less than 8%) of the administered dose appears in the urine, primarily as metabolites. Less than 1% of the parent drug is recovered in faeces.

5.3 Preclinical safety data
Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Povidone
Sodium lauril sulfate
Butylhydroxyanisole
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline (E460)
Maize starch
Meglumine
Croscarmellose sodium
Polacrilin potassium
Magnesium stearate
Silica, colloidal anhydrous
Iron oxide yellow (E172) [1mg tablets only]

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Blister packs: 2 years
HDPE bottle packs: 2 years. Once opened use within 3 months.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Aluminium/Aluminium blisters in an outer carton (pack sizes of 30, 90, 120, 180, 200 and 270 tablets), or HDPE bottles with PP (Polypropylene) closure and desiccant (containing 120, 200 and 270 tablets). Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Chanelle Medical
Loughrea, Co. Galway, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 13931/0058

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/05/2012

10 DATE OF REVISION OF THE TEXT
23/05/2012
1 NAME OF THE MEDICINAL PRODUCT
Repaglinide Chanelle Medical 2 mg Tablets

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

Excipient(s):
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

2 mg: Peach coloured, round, biconvex tablets debossed with ‘M’ on one side of the tablet and ‘R23’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Repaglinide is indicated in patients with type 2 diabetes (Non Insulin-Dependent Diabetes Mellitus (NIDDM)) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in type 2 diabetes patients who are not satisfactorily controlled on metformin alone.

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

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

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

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

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

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

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

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

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

Maintenance
The recommended maximum single dose is 4 mg taken with main meals. The total maximum daily dose should not exceed 16 mg.
Specific patient groups
Repaglinide is primarily excreted via the bile and excretion is therefore not affected by renal disorders. Eight percent of one dose of repaglinide is excreted through the kidneys and total plasma clearance of the product is decreased in patients with renal impairment. As insulin sensitivity is increased in diabetic patients with renal impairment, caution is advised when titrating these patients.

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

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

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

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

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

4.3 Contraindications
- Hypersensitivity to repaglinide or to any of the excipients in Prandin.
- 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, ciclosporin, clarithromycin, itraconazole, ketoconazole, trimethoprim, other antidiabetic agents, monoamine oxidase inhibitors (MAOI), non selective beta blocking agents, angiotensin converting enzyme (ACE)-inhibitors, salicylates, NSAIDs, octreotide, alcohol, and anabolic steroids.

Co-administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and repaglinide (a single dose of 0.25 mg) increased the repaglinide AUC 8.1-fold and C<sub>max</sub> 2.4-fold in healthy volunteers. Half-life was prolonged from 1.3 hr to 3.7 hr, resulting in possibly enhanced and prolonged blood glucose-lowering effect of repaglinide, and plasma repaglinide concentration at 7 hr was increased 28.6-fold by gemfibrozil. The concomitant use of gemfibrozil and repaglinide is contraindicated (see section 4.3).

Co-administration of trimethoprim (160 mg twice daily), a moderate CYP2C8 inhibitor, and repaglinide (a single dose of 0.25 mg) increased the repaglinide AUC, C<sub>max</sub> and t<sub>1/2</sub> (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.

In a study conducted in healthy volunteers, the concomitant administration of repaglinide (a single dose of 0.25 mg) and ciclosporin (repeated dose at 100 mg) increased repaglinide AUC and Cmax about 2.5-fold and 1.8-fold respectively. Since the interaction has not been established with dosages higher than 0.25 mg for repaglinide, the concomitant use of ciclosporin with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4).

β-blocking agents may mask the symptoms of hypoglycaemia.

Co-administration of cimetidine, nifedipine, oestrogen, or simvastatin with repaglinide, all CYP3A4 substrates, did not significantly alter the pharmacokinetic parameters of repaglinide.

Repaglinide had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline or warfarin at steady state, when administered to healthy volunteers. Dosage adjustment of these compounds when co-administered with repaglinide is therefore not necessary.

The following substances may reduce the hypoglycaemic effect of repaglinide: Oral contraceptives, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.

When these medications are administered to or withdrawn from a patient receiving repaglinide, the patient should be observed closely for changes in glycaemic control.

When repaglinide is used together with other drugs that are mainly secreted by the bile, like repaglinide, any potential interaction should be considered.

4.6 Fertility pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Based on the experience with repaglinide and with other hypoglycaemic agents the following adverse events have been seen: Frequencies are defined as: Common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 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 of the chemical structure.

**Eye disorders**
Very rare: Visual disturbances.

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

**Cardiac disorders**
Rare: Cardiovascular disease.

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

**Hepato-biliary disorders**
Very rare: Hepatic function abnormal.

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

Very rare: Increased liver enzymes.

Isolated cases of increase in liver enzymes have been reported during treatment with repaglinide. Most cases were mild and transient, and very few patients discontinued treatment due to increase in liver enzymes.
4.9 Overdose
Repaglinide has been given with weekly escalating doses from 4 - 20 mg four times daily in a 6-week period. No safety concerns were raised. As hypoglycaemia in this study was avoided through increased calorie intake, a relative overdose may result in an exaggerated glucose lowering effect with development of hypoglycaemic symptoms (dizziness, sweating, tremor, headache etc.). Should these symptoms occur, adequate action should be taken to correct the low blood glucose (oral carbohydrates). More severe hypoglycaemia with seizure, loss of consciousness or coma should be treated with IV glucose.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmaco-therapeutic group: Carbamoylmethyl benzoic acid derivative, ATC code: A10B X02.

Repaglinide is a novel short-acting oral secretagogue. Repaglinide lowers the blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β-cells in the pancreatic islets.

Repaglinide closes ATP-dependent potassium channels in the β-cell membrane via a target protein different from other secretagogues. This depolarises the β-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the β-cell.

In type 2 diabetic patients, the insulinotropic response to a meal occurred within 30 minutes after an oral dose of repaglinide. This resulted in a blood glucose-lowering effect throughout the meal period. The elevated insulin levels did not persist beyond the time of the meal challenge. Plasma repaglinide levels decreased rapidly, and low drug concentrations were seen in the plasma of type 2 diabetic patients 4 hours post-administration.

A dose-dependent decrease in blood glucose was demonstrated in type 2 diabetic patients when administered in doses from 0.5 to 4 mg repaglinide.

Clinical study results have shown that repaglinide is optimally dosed in relation to main meals (preprandial dosing).

Doses are usually taken within 15 minutes of the meal, but the time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

One epidemiological study suggested an increased risk of acute coronary syndrome in repaglinide treated patients as compared to sulfonylurea treated patients (see sections 4.4 and 4.8).

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

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

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

A high interindividual variability (60%) in repaglinide plasma concentrations has been detected in the clinical trials. Intraindividual variability is low to moderate (35%) and as repaglinide should be titrated against the clinical response, efficacy is not affected by interindividual variability.

Repaglinide exposure is increased in patients with hepatic insufficiency and in the elderly type 2 diabetic patients. The AUC (SD) after 2 mg single dose exposure (4 mg in patients with hepatic insufficiency) was 31.4 ng/ml x hr (28.3) in healthy volunteers, 304.9 ng/ml x hr (228.0) in patients with hepatic insufficiency, and 117.9 ng/ml x hr (83.8) in the elderly type 2 diabetic patients. After a 5 day treatment of repaglinide (2 mg x 3/day) in patients with a severe impaired renal function (creatinine clearance: 20-39 ml/min.), the results showed a significant 2-fold increase of the exposure (AUC) and half-life (t1/2) as compared to subjects with normal renal function.
Repaglinide is highly bound to plasma proteins in humans (greater than 98%).

No clinically relevant differences were seen in the pharmacokinetics of repaglinide, when repaglinide was administered 0, 15 or 30 minutes before a meal or in a 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
Povidone
Sodium lauril sulfate
Butylhydroxyanisole
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline (E460)
Maize starch
Meglumine
Croscarmellose sodium
Polacrilin potassium
Magnesium stearate
Silica, colloidal anhydrous
Iron oxide red (E172) [2 mg tablets only]

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Blister packs: 2 years
HDPE bottle packs: 2 years. Once opened use within 3 months.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Aluminium/Aluminium blisters in an outer carton (pack sizes of 30, 90, 120, 180, 200 and 270 tablets), or HDPE bottles with PP (Polypropylene) closure and desiccant (containing 120, 200 and 270 tablets). Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Chanelle Medical
Loughrea, Co. Galway, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 13931/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/05/2012

10 DATE OF REVISION OF THE TEXT
23/05/2012
REPAGLINIDE

0.5 mg, 1 mg, 2 mg TABLETS
(paraglinide)

Read all of this leaflet carefully before you start taking 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 REPA GLINIDE 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 in your blood or 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 addition 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 TAKE REPA GLINIDE

Do not take Repaglinide if you:
- are allergic (hypersensitive) to repaglinide or any of the other ingredients of this medicine
- suffer from type 1 (insulin dependent) diabetes
- have been diagnosed with raised body fluid levels (a condition known as diabetic ketoacidosis)
- suffer from severe liver disease
- take glibenclamide (used to lower increased fat levels in the blood).

If any of these apply to you, tell your doctor and do not take Repaglinide.

Take special care with Repaglinide:
- if you suffer from liver problems, repaglinide is not recommended if you have moderate liver disease and should not be taken if you have severe liver disease (see Do not take Repaglinide).
- if you have kidney problems, repaglinide should be taken with caution.
- if you have recently had major surgery or suffered from a severe illness or infection because your body’s glycemic control may have been affected. In these cases your doctor may advise you to stop taking repaglinide and prandin insulin until your blood sugar levels have stabilized.
- if you are under 18 or over 75 years of age, repaglinide is recommended. It has not been studied in these age groups.
- tell your doctor or nurse if you are allergic (hypersensitive) to 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 hypoglycaemic reaction and symptoms of low blood sugars) 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 sweats; cool pale skin
- headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness or weakness; numbness or tingling in your hands or feet; 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 wait.

When the symptoms of hypoglycaemia have disappeared or when your blood sugar levels are stabilised continue with your repaglinide treatment.

Tell people you have diabetes and 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 be too late.

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 hypos, 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 infection 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. Ask your doctor. The amount of repaglinide, food or exercise may need to be adjusted.

Taking other medicines:
You can take repaglinide with metformin (another medicine for diabetes) if your doctor prescribes it. If you are already taking another medicine for your diabetes and you are also prescribed repaglinide, please tell your doctor before you start to take this medicine.

Do not take repaglinide if you are already taking glibenclamide to lower fat levels in your blood.

Your body’s response to repaglinide may change if you are also taking any of the following medicines:
- monamine oxidase inhibitors (MAO) used to treat depression
- beta blockers used to treat high blood pressure or heart conditions
- ACE inhibitors used to treat heart conditions
- anti-inflammatory drugs (NSAIDs) used as painkillers
- antidepressants used to treat some cancers
- steroids (both synthetic steroids and corticosteroids) used to treat asthma or inflammation
- oral contraceptives
- thiazides (used as diuretics or water pills)
- dextrose to treat breast cancer and endometriosis
- thyroid products (used to treat low levels of thyroid hormones)
- sympathomimetics used to treat asthma
- chemotherapy, tricyclics or other antidepressants to treat bacterial infections (antibiotics)
- gemfibrozil (used to treat high blood fats)
- gliclazide (used to suppress the immune system)
- imipramine or ketocapride to treat fungal infections
- phenytoin, carbamazepine or Phenytoin to treat epilepsy
- St John’s worth, a herbal medicine.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Repaglinide with food and drink:
Take Repaglinide before main meals.
Alcohol can alter the way this medicine works to reduce your blood sugar levels. You should watch for the signs or symptoms of hypo (low blood sugar levels) if you consume alcohol.
PAR Repaglinide Chanelle Medical 0.5 mg, 1 mg and 2 mg Tablets

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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Your ability to drive or operate a machine may be affected if your blood sugar is low or high. Be in mind that you could endanger yourself or others. Please ask your doctor whether you can drive a car if you:
- have frequent hypo
- have few or no warning signs of hypo.

3. HOW TO TAKE REPAGLINDIDE

Always take Repaglinide exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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 60 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 60 minutes before each main meal. The maximum recommended daily dose is 16 mg.

Use in children and adolescents
Repaglinide is not recommended for children and adolescents under 18 years of age.

If you take more Repaglinide than you should
If you take too many tablets your blood sugar levels may become too low leading to hypo (hypoglycaemia). 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 to make up for the missed 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 treatment is necessary contact your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

Common side effects (may effect up to 1 in 10 patients):
- low blood sugar (hypoglycaemia), see 'If you get a hypo'. The risk of getting a hypo may increase if you take other medicines
- stomach pain
- diarrhoea.

Rare side effects (may effect up to 1 in 1000 patients):
- acute coronary syndrome (but it may not be due to the drug).

Very rare side effects (may effect up to 1 in 10,000 patients):
- allergy (for example swelling, difficulty breathing, rapid heartbeat, feeling dizzy and sweating which could be signs of anaphylactic reaction). Contact a doctor immediately
- vomiting
- confusion
- visual disturbances
- severe liver problems including abnormal liver function and raised liver enzymes in the blood.

Not known (cannot be estimated from the available data):
- hypoglycaemic coma or unconsciousness (very severe hypoglycaemic reactions – see if you get a hypo). Contact a doctor immediately
- feeling sick (nausea)
- hypersensitivity (such as rash, itchy skin, reddening of the skin, swelling of the skin).

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.

5. HOW TO STORE REPAGLINDIDE

Keep out of the reach and sight of children.

Do not use Repaglinide after the expiry date, which is stated on the blister, carton or bottle label after EXP. The expiry date refers to the last day of that month.

Repaglinide supplied in HDPE bottle packs should be used for no longer than 3 months after the bottle has first been opened.

This medicinal product does not require any special storage conditions.

Do not use Repaglinide if you notice any discoloration of the tablets.

Medicines should not be disposed of via wastewater or household waste. 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. Each tablet contains 0.5 mg, 1 mg, 2 mg of repaglinide.

The other ingredients are povidone, sodium lauril sulphate, hydroxypropylmethylcellulose, calcium hydrogen phosphate, anhydrous, cellulose, microcrystalline (E460), maize, gum arabic, magnesium stearate, silica, colloidal anhydrous, iron oxide yellow (E172) (1 mg tablets only), iron oxide red (E172) (2 mg tablets only).

What Repaglinide looks like and contents of the pack
The 0.5 mg tablets are white to off-white, round, biconvex tablets debossed with 'M' on one side of the tablet and 'R21' on the other side.

The 1 mg tablets are yellow, round, biconvex tablets debossed with 'M' on one side of the tablet and 'R22' on the other side.

The 2 mg tablets are peach-coloured, round, biconvex tablets debossed with 'M' on one side of the tablet and 'R13' on the other side.

The medicinal product is available in blister packs of 30, 50, 120, 180, 200 and 270 or bottles containing 120, 209 and 270 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Chanelle Medical, Loughrea, Co. Galway, Ireland.

Manufacturer:
Gencor Laboratories, 35/36 Baldroye Industrial Estate, Grange Road, Dublin 11, Ireland.
Module 4

Labelling
PAR Repaglinide Chanelle Medical 0.5 mg, 1 mg and 2 mg Tablets

Each tablet contains 1 mg of repaglinide.

Directions: As directed by a doctor. For oral use. Read the enclosed leaflet. Keep out of the reach and sight of children.

PL 1793/1998 Mylan
Pi, Holder: Channel Medical, Loughrea, Co. Galway, Ireland.
Distributor: Mylan, Queens Bar, Harfordshire, EN1 1TL, United Kingdom.
Module 5
Scientific discussion during initial procedure

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Repaglinide Chanelle Medical 0.5, 1 and 2 mg Tablets in the treatment of type 2 diabetes (Non Insulin-Dependent Diabetes Mellitus (NIDDM)) could be approved.

These applications are for Repaglinide Chanelle Medical 0.5, 1 and 2 mg Tablets submitted under Article 10.1 of Directive 2001/83/EC as amended. The applications refer to NovoNorm 0.5 mg, 1 mg and 2 mg tablets (EM 04668/0040, 41 and 44), authorised to Novo Nordisk A/S, and registered via centralised procedure in the EU since 17th August 1998. The reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the RMS in these Decentralised Procedures (UK/H/2573/001-3/DC), Chanelle Medical applied for the Marketing Authorisations for Repaglinide Chanelle Medical 0.5, 1 and 2 mg Tablets in Belgium, Germany, Finland, France, Italy, Luxembourg, Romania, Spain and Sweden.

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.

Repaglinide is a novel short-acting oral secretagogue. It lowers the blood glucose levels 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.

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

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites within and outside the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The RMS considers that 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 non-submission of a Risk Management Plan.

All Member States agreed to grant licences for the above products at the end of procedure (Day 210 – 25th April 2012). After a subsequent national phase, the UK granted a licence for these products on 23rd May 2012 (PL 13931/0057-9).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Repaglinide Chanelle Medical 0.5, 1 and 2 mg Tablets</th>
</tr>
</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>A10BX02 Carboxamoylmethyl benzoic acid derivative</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Tablets 0.5, 1 and 2 mg</td>
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<tr>
<td>Reference numbers for the Decentralised Procedures</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<tr>
<td>Concerned Member States</td>
<td>Belgium, Germany, Finland, France, Italy, Luxembourg, Romania, Spain and Sweden.</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 13931/0057-9</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Chanelle Medical Loughrea, Co. Galway, Ireland</td>
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</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Repaglinide

Chemical Name: 2-Ethoxy-4-[[2-[(1S)-3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl]amino]-2-oxoethyl]benzoic acid.

Structure:

![Chemical Structure Image]

Molecular Formula: C_{27}H_{36}N_{2}O_{4}
Molecular Weight: 452.59

Appearance: A white to almost white powder, practically insoluble in water, freely soluble in methanol and dichloromethane.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients povidone, sodium lauril sulphate, butylhydroxyanisole, calcium hydrogen phosphate, anhydrous, cellulose, microcrystalline (E460), maize starch, meglumine, croscarmellose sodium, polacrilin potassium, magnesium stearate and silica, colloidal anhydrous.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of sodium lauril sulphate and magnesium stearate which comply with an in house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has stated that none of the excipients are of animal or human origin, and confirms that the magnesium stearate used is of vegetable origin.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for these applications. Comparable dissolution and impurity profile are provided for these products versus the originator products.

Comparative impurity and dissolution profiles have been presented for the test and reference products.
Manufacture
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in Aluminium/Aluminium blisters, available in packs of 30, 90, 120, 180, 200 and 270 tablets, or HDPE bottles with Polypropylene closure and desiccant containing 120, 200 and 270 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with no special storage conditions are set. This is satisfactory. The HDPE bottles should be used within 3 months once it is opened.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.
Marketing Authorisation Application (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 aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of repaglinide are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

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

There are no objections to the approval of these products from a non-clinical point of view.

III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY
To support these applications, the applicant has submitted a bioequivalence study under fasting conditions comparing the test product with the reference product.

STUDY 248-10
This was an open-label, randomised, two-treatment, two sequences, four-period, , crossover (replicate design) bioavailability and bioequivalence study of Repaglinide 2 mg Tablets (Matrix Laboratories Limited) versus Prandin 2 mg Tablets (Novo Nordisk A/S, Denmark) in healthy adult human subjects under pre-prandial conditions.

Blood samples were collected before dosing and at 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.53, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00 and 12.00 hours after drug administration was carried out in each group. A washout period of 4 days was maintained between the two dosing days.

Results
Pharmacokinetic parameters of Repaglinide (log transformed) n=35

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Least Squares Means (ng/mL)</th>
<th>Point Estimate (%)</th>
<th>90% Confidence Interval</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>Test (T) 20.8341, Reference (R) 19.2560</td>
<td>108.20</td>
<td>97.04 - 120.64</td>
<td>95.8</td>
</tr>
<tr>
<td>AUC0-t</td>
<td>Test (T) 55.4315, Reference (R) 54.6591</td>
<td>101.41</td>
<td>96.99 - 106.04</td>
<td>100.0</td>
</tr>
</tbody>
</table>
The results show that the 90% confidence intervals for \( \text{AUC}_{0-t} \) and \( \text{C}_{\text{max}} \) fell within the acceptable range (80-125%). Bioequivalence has been demonstrated between the test formulation (Repaglinide 2 mg Tablets) and the reference formulation (Prandin 2 mg Tablets).

As the 0.5 mg and 1 mg strengths of the product meet the bio-waiver criteria specified in the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CHMP/EWP/QWP/1401/98 Rev.1), the results and conclusions of the bioequivalence study on the 2 mg strength can be extrapolated to the 0.5 mg and 1 mg Tablets.

**Efficacy**
No new efficacy data have been submitted and none are required for these applications.

**Safety**
No new safety data have been submitted and none are required for these applications.

**Expert Report**
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Summary of Product Characteristics**
These are satisfactory.

**Patient Information Leaflet**
These are satisfactory.

**Labelling**
These are satisfactory.

**MAA Forms**
These are satisfactory.

**Conclusions**
There are no objections to the approval of these products from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Repaglinide 0.5, 1 and 2 mg 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 benefit/risk balance.

NON-CLINICAL
No new Non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Repaglinide 2 mg Tablets and the reference product, Prandin 2 mg Tablets. As the 0.5 mg and 1 mg strengths of the product meet the bio-waiver criteria specified in the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CHMP/EWP/QWP/1401/98 Rev.1), the results and conclusions of the bioequivalence study on the 2 mg strength can be extrapolated to the 0.5 mg and 1 mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs and PIL are satisfactory and consistent with those of the reference products. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. 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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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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