# SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Prandin. For information on changes after approval please refer to module 8.**

## 1. Introduction

Prandin contains Repaglinide. Repaglinide is a carbamoylmethyl benzoic acid derivative insulinotropic agent, intended for use in the treatment of NIDDM (Non-Insulin-Dependent Diabetes Mellitus).

Existing treatment of NIDDM aims to increase glucose disposal via improving glucose sensitivity (metformin), reducing glucose uptake (acarbose), improving insulin sensitivity (rosiglitazone, pioglitazone), substituting insulin (insulin injections) or inducing insulin secretion (sulphonylureas). Similar to the latter group, repaglinide lowers the blood glucose levels acutely by stimulating the release of insulin from the pancreas. Repaglinide is structurally unrelated to sulfonylureas (such as glibenclamide) and the molecular mechanism of induction of insulin release is different.

The approved indication is for the treatment of 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.

The recommended starting dose is 0.5 mg. One or two weeks should elapse between titration steps as determined by blood glucose response. The recommend maximum single dose is 4 mg taken with main meals. The total maximum daily dose should not exceed 16 mg.

## 2. Chemical, pharmaceutical and biological aspects

### Composition

Prandin is presented as an immediate release, conventional tablet formulation. Standard pharmacopoeial-grade excipients are used where appropriate, in order to optimise the stability and release of the active substance. A blend of standard excipients such as disintegrants, lubricants etc. ensures that the disintegration of the tablet is rapid and subsequent dissolution of the active substance is also rapid and uniform. A number of formulations have been developed and used in clinical trials during the history of the product, although these have been shown to be bioequivalent in crossover studies in humans.

As applied for, the marketing application is for three strengths (0.5 mg, 1.0 mg and 2.0 mg). The 0.5 mg tablets are white, the 1.0 mg tablets are yellow and the 2.0 mg tablets are peach-coloured.

The manufacturing process has remained essentially unchanged during development and involves a spray-drying granulation process for optimum distribution of the active substance in the matrix of the tablet.

### Active substance

Repaglinide is a new chemical entity with a non-sulphonylurea structure. It is a chiral molecule synthesised essentially as the S(+)-isomer, with traces of the R(-)-isomer present as an impurity. This selective synthesis has been developed on the grounds that the S(+)-isomer is approximately 100-fold more potent than the R(-)-enantiomer in the rat. The synthesis involves two parallel pathways that have been adequately described.

The active substance exists in different polymorphic forms, although this is without relevance for the drug product as repaglinide is dissolved during the manufacture of the product. Similarly, the particle size distribution of the drug substance is of no concern in this case.

Generally, the active substance specification has been justified and is considered to provide adequate control of the drug substance with regard to safety (impurity levels) and bioavailablility. The batch analytical data presented confirm reproducible and consistent synthesis, and the data are in agreement with the proposed specification. Control methods have been adequately described and are generally well validated.

Stability data support the retest period of the active substance that is 5 years.

**Other ingredients**

The excipients are well established as suitable for use in pharmaceutical products and are described in Pharmacopoeias.

The packaging proposed for marketing, Al/Al/PVC-blister and HDP containers with PP screw cap, is adequate. The package form is chosen on the basis of the sensitivity of the tablets to high relative humidity. Compatibility of packaging and formulation is further established by the relevant stability studies.

**Product development and finished product**

The manufacturing process for the three strengths of repaglinide tablets is very similar. The major step in the manufacturing process of the tablets is the formulation of spray dried granules. Equipment and manufacturing process are adequately described. Process validation was adequately presented in the dossier and indicates that the manufacturing process is under control.

Satisfactory batch release and shelf life specifications have been proposed and justified.

Tests at release are standard and include limits for assay, related impurities (including enantiomer), disintegration, dissolution, uniformity of content etc. These tests and limits should ensure consistent clinical performance of the product.

**Stability of the product**

Stability studies have been performed under stressed, accelerated and ambient long term conditions, according to current ICH recommendations. Analysis has been performed by validated stability-indicating methods and has focussed on chiral aspects of the degradation process (racemisation) as well as degradation in general and changes in disintegration/dissolution.

The results of these studies were analysed and in general they confirm the suitability of the packaging material and the shelf-life and storage conditions as proposed in the SPC (see sections 6.3, 6.4 and 6.5 of the SPC)

## 3. Toxico-pharmacological aspects

The marketing authorisation holder of NovoNorm tablets, Novo Nordisk A/S, Denmark, consented to the toxico-pharmacological data contained in the original file for NovoNorm being used for the purpose examining this application.

**Pharmacodynamics**

The antihyperglycemic activity of repaglinide has been adequately studied in rats and dogs. Comparative studies were performed with glibenclamide. Repaglinide was found to have a potent blood sugar lowering effect with an oral ED50 of about 0.01 mg/kg. The racemate was 2-fold less active and the other enantiomer was 100-fold less active than repaglinide. At equimolar doses repaglinide is 5-15 times (depending on the used model) more potent than glibenclamide in reducing glucose levels. Metabolite M-12 has at relevant doses (0.03-1.0mg/kg) similar hypoglycemic activity as the parent compound with exception for a delayed onset of action at lower doses.

From various pre-clinical studies it can be concluded that it is unlikely that repaglinide at clinically relevant doses has effects on the nervous, gastro-intestinal and respiratory system.

With regard to the cardiovascular system, repaglinide showed substantial and not explainable species differences. In rats repaglinide increased blood pressure, whereas, after comparable doses in rabbits, a decrease in blood pressure was observed. An effect on blood pressure occurs at a dose about 100 times

the dose that causes a hypoglycaemic effect. In rabbits no effects on the ECG were noted. In isolated single guinea pig ventricular myocytes using the patch clamp technique, repaglinide (1 and 10μmol/l) shortened the action potential at 90% of repolarisation.

**Pharmacokinetics**

Repaglinide was rapidly absorbed after oral administration in rats. The absolute bioavailability of 1 mg/kg repaglinide in rats and dogs ranged from 48% to 73%. The absolute bioavailability in man was 63%.

The calculated ratio AUC animal/human was 19 and 22 for males and females, respectively and the safety margins are considered sufficient. Protein binding was high (96-98.6%). Studies on distribution of repaglinide and its metabolites in rats indicated rapid and wide distribution to various tissues, including brain. The highest concentrations of repaglinide and its metabolites are found in the liver and gastrointestinal tract, which is consistent with metabolism and high faecal elimination.

Human metabolism is similar to that in animals. There was, however, one metabolite in humans that could not be fully assessed pre-clinically because of low amounts being formed in animals. This metabolite identified as M10 is found in human urine and plasma at low concentrations (2% of administered dose)and therefore it is unlikely to represent a potential safety concern in humans.

**Toxicology**

The main findings in the toxicology studies were liver enlargement in the dog study at dosage resulting in plasma concentrations of 600 times human $C_{max.}$ In addition, increased testes weight in the carcinogenicity study was observed at dose levels resulting in exposure levels of >30 times human maximum therapeutic response exposure levels (HMTL). The majority of effects seen in the experimental animals might be attributed to the pharmacodynamic effect of repaglinide.

Tumourigenic findings might be considered to be of epigenetic origin and/or species specific (thyroid findings). As these lesions could only be observed at dose levels corresponding to exposure levels >30 times HMTL the findings are considered to pose no risk for humans. As no other major adverse effects are observed at dose levels corresponding to exposure levels prominently higher than the HMTL or human $C_{max}$-values, margins of safety may be regarded to be adequate.

## 4. Clinical aspects

The marketing authorisation holder of NovoNorm tablets, Novo Nordisk A/S, Denmark, consented to the clinical data contained in the original file for NovoNorm being used for the purpose examining this application.

**Clinical Pharmacology**

A total of 61 studies were performed, 45 clinical pharmacology studies and 16 clinical trials.

A total of 2156 patients were exposed to repaglinide in all trials combined. In the assessment it was noted that there were nine adequate, well-controlled trials comprising 1563 patients.

In the adequate and well-controlled studies, 399 patients >65 years received the drug at any dose and 343 of these patients were exposed in the long-term controlled studies.

**Pharmacodynamics**

Repaglinide lowers blood glucose acutely by stimulating the release of insulin from the pancreas.

In NIDDM patients dose-escalating studies established a clinically significant dose response in the range from 0.5 mg to 4 mg given three times preprandially. In one double-blind, placebo controlled study recruiting 24 patients over 5 days treatment, the 0.25mg did not significantly (i.e. significance was defined as at least a 15% reduction in glucose AUC (0-24h)) change blood glucose levels but achieved a mean reduction of 12.5%.

Further studies suggested that repaglinide should be taken two to four times a day in connection with meals. One study suggested insufficient overall glycaemic control when two doses were combined with three meals.

Dose-tolerability data derived from 3 pharmacodynamic studies (62 diabetic patients) with doses up to 20 mg, 4 times daily revealed headache (14 patients) and gastro-intestinal (90 patients) events as the most frequent complaints. One patient had abnormal ECG results (non-specific ST-T changes) but there were no episodes of hypoglycaemia or serious events.

**Pharmacokinetics**

Repaglinide is rapidly absorbed ($t_{max}$ 0.9-1.4h; $t_{1/2}$ 0.6-1.4h) with an absolute bioavailability of 67.5 +/- 23.5%. Repaglinide is almost completely metabolised to oxidative metabolites and/or glucuronide conjugates. The elimination half-life is about 1 h. Metabolites are mainly excreted by faeces (90%) and to a lesser extent by urine (8%). Repaglinide did not accumulate after dose regimens of three or four times a day. Plasma concentrations of repaglinide are dose-proportional within the range of 0.125 to 20 mg three or four times daily. A very high inter-individual variability is seen in plasma levels of repaglinide, whereas intra-individual variability was low to moderate. The cause for the high inter-individual variability is not known and is reflected in the pharmacodynamic effects so that for a patient who has a high repaglinide AUC, efficacy is reached at a lower dose. In addition, the results of the maximum tolerated-dose trial showed that the safety margin for repaglinide was large.

Pharmacokinetics were evaluated in patients with mild/moderate and severely impaired renal function and on haemodialysis as well as in patients with hepatic impairment. These studies indicated that repaglinide exposure is increased in patients with hepatic insufficiency (see section 5.2 of the SPC, “Pharmacokinetic properties”). The mean AUC levels and SD - as investigated in 24 patients were: 92 +/-67 (12 healthy patients), 311 +/-160 (9 class B patients = moderate impairment) and 543 (3 class C patients = severe impairment). After a 5 day treatment of repaglinide (2 mg, three times a 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 as compared to subjects with normal renal function (see section 5.2 of the SPC, “Pharmacokinetic properties”).In healthy elderly (>65 years) individuals, the pharmacokinetics were comparable to those in young subjects although higher exposure pertained to elderly patients with Type 2 diabetes versus healthy elderly, i.e. AUC at day 9 were 87 (34-110) and 231 (14-973) in healthy elderly and elderly with Type 2 diabetes. It could not be determined whether higher mean values in elderly are due to age, illness or the large interindividual variability.

There were no trials performed in children or adolescents <18 years of age or in elderly >75 years of age.

Interaction studies

Repaglinide, the active compound of Prandin, is extensively metabolised. In vitro studies showed that the cytochrome P450 iso-enzyme 3A4 is solely responsible for the oxidative metabolism of repaglinide. The involvement of CYP 3A4 in repaglinide biotrasformation was investigated in five clinical trials in healthy subjects. These five interaction studies were performed with compounds, that are substrates, inducers of inhibitors of CYP 3A4 in order to elucidate the role of this iso-enzym in the pharmacokinetics of repaglinide. The results of these studies demonstrate that inducers, inhibitors or substrates of CYP 3A4 iso-enzymes do not influence the pharmacokinetics of repaglinide to a clinically relevant extent. Also, the concomitant administration of repaglinide did not change the pharmakokinetics of ethinylestradiol and nifedipine, two compounds predominately metabolised by CYP 3A4. However there is some influence on the Cmax of simvastatin and rifampicin (see section 4.5 of the SPC, “Interaction with other medicinal products and other forms of interaction”).

The pharmacokinetic interaction data described in the SPC were substantiated in 4 interaction studies performed in healthy volunteers receiving 2 mg repaglinide three times a day.

**Clinical efficacy**

In the well-controlled studies, Type 2 diabetic patients were treated by diet and/or oral hypoglycaemic agents. Treatment with insulin was an exclusion criterion. The dosage was generally 0.5 to 4 mg 3

times daily. In the two placebo controlled studies dosages from 0.25 to 8 mg 3 times daily were used. Three sulphonylureas were used as comparators: glibenclamide, gliclazide and glipzide. In one study the effect of adding repaglinide to metformin was investigated.Change from baseline in $HbA_{1c}$ and fasting plasma glucose (FPG) were the main efficacy endpoints. The effects of a number of baseline covariates, such as previous antidiabetic treatment, $HbA_{1c}$ and Body Mass Index at baseline, duration of diabetes, fasting C-peptide, $HbA_{1c}$ at baseline by previous oral hypoglycaemic agents, were analysed.

The primary analysis was based on change from baseline to the last visit (ITT and last observation carried forward). In the equivalence trials the criterion for non-inferiority was that the upper limit for the 95% confidence interval for the difference (repaglinide-active comparator) in mean $HbA_{1c}$ was less than 0.6% units.

The five long-term protocols were identical in design, inclusion/exclusion criteria, titration procedures, and primary efficacy and safety variables. In order to collect more safety data on repaglinide, the randomisation was 2:1 (repaglinide:comparator). All patients were switched from their previous treatment to the test compound with no washout period. They were treated in an 8-week titration period followed by a 12-month maintenance period. All studies were performed according to Good Clinical Practice and the Declaration of Helsinki with local Ethics Committee approval.

**Dose-response studies and Main Clinical Studies**

Placebo-controlled studies

Dose titration followed by a three-month maintenance period was performed in a parallel, double blind trial in 99 Type 2 diabetic patients. $HbA_{1c}$ increased significantly in the placebo group (+1.1%), and decreased significantly in the repaglinide group (-0.6%) when compared with baseline values. The changes in fasting plasma glucose were on average -1.5 mmol/l and in post-prandial plasma glucose -2.6 mmol/l with repaglinide treatment, and +1.5 mmol/l and +2.9 mmol/l, repectively with placebo. One aim in this study was to explore possible additional effects by increasing the dose to from 4 mg to 8 mg tid. Twenty-four of 66 patients on repaglinide reached the 8 mg dose level and 16 of these 24 patients were titrated back down to 4 mg.

**Dose response study**

In another parallel, double blind dose response study randomising 145 patients, the aim was to show a dose response over four weeks and ensure that glycaemic control was in steady state within the two weeks recommended for dose titration in the phase III programme. Efficacy was calculated based on the AUC of 24-hour blood glucose. The lowest effective dose was 0.25 mg as indicated in table 1 below:

Table 1: Dose-response relations at steady state in Type 2 diabetic patients.

| Endpoint | Placebo | 0.25 mg | 0.5 mg | 1.0 mg | 2.0 mg | 4.0 mg |
|---|---|---|---|---|---|---|
| BGmean* mg/dl: | | | | | | |
| at baseline | 244.2 | 241.2 | 255.9 | 239.5 | 230.9 | 254.3 |
| at steady state | 239.3 | 195.5 | 199.0 | 177.5 | 172.8 | 170.2 |
| from baseline to steady state | -4.9 (2%) | -45.7 (18.9%) | -56.9 (22.2%) | -62.0 (25.9%) | 58.1 (25.2%) | -84.1 (33.1%) |
| time to steady state, weeks | - | 2 | 2 | 3 | 1 | 3 |

* BGmean = The mean area under the curve under the 24-hour profile divided by time.

However, the 0.250 mg dose was judged not to be the clinically relevant dose for long-term treatment because randomisation allowed a relatively high proportion of treatment naive patients to this group (35%). This was regarded to overestimate the treatment effect in this dose group and it was therefore decided the recommended starting dose and the upper limit for the dose preprandially were set at 0.5 mg and 4 mg, respectively in the confirmatory trials.

**Main studies**

Active-controlled studies

*Medium-term studies*

One study (n=195) with repaglinide in comparison with glibenclamide showed a decrease by 0.3% and 0.4% respectively for $HbA_{1c}$ after 10 weeks of maintenance therapy.

In the second medium-term study recruiting 83 diabetic patients, randomised to repaglinide, metformin or the combination of the two drugs (n=27), $HbA_{1c}$ was equally reduced (-0.38 and -0.33) after 6 months in the two monotherapy arms, whereas the reduction (-1.41%) in the combination arm was at least additive. In addition to the improved efficacy in the combination arm of this study it was noted that the combination repaglinide and metformin conferred an increased risk of hypoglycaemia: No patients treated with metformin, 3 patients treated with repaglinide and 9 patients treated with the combination experienced hypoglycaemic reactions.

*Long-term studies*

The total number of patients included in these five studies was 1796: 1209 on repaglinide, 407 on glibenclamide, 81 on glipizide and 99 on gliclazide. The withdrawal rates were about 33 percent for all drugs used (table 2).

Table 2: Patient disposition in the five long-term studies.

| | Repaglinide N=1209 (100%) | Glibenclamide N=407 (100%) | Gliclazide N=99 (100%) | Glipzide N=81 (100%) |
|---|---|---|---|---|
| Withdrawals | 412 (34%) | 136 (33%) | 31 (31%) | 23 (28%) |
| Adverse events | 163 (13%) | 53 (13%) | 11 (11%) | 16 (20%) |
| Ineffective therapy | 63 (5%) | 16 (4%) | 10 (10%) | 2 (2%) |
| Non-compliance | 74 (6%) | 35 (9%) | 0 (0%) | 1 (1%) |
| Other | 112 (9%) | 32 (9%) | 10 (10%) | 4 (5%) |

In these trials (four of 1 year and one of 3 months duration) the efficacy of repaglinide was confirmed. The initial dosage of repaglinide was 0.5, 1.0 or 2.0 mg three times daily preprandially.

In general, levels of $HbA_{1c}$ and FBG decreased in the early weeks of treatment. Thereafter, a deterioration was seen. Results with the different active comparators are seen in table 3.

Table 3:

| Change from Baseline to last visit ($HbA_{1c}$) | | | | |
|---|---|---|---|---|
| Treatment/Difference | N | Mean | (95% C.I.) | p-value |
| REP | 338 | 0.09 | -0.06; 0.24 | 0.2498 |
| GLIB | 171 | 0.10 | -0.11; 0.31 | 0.3399 |
| REP- GLIB | | -0.01 | -.0.26; 0.23 | 0.9243 |
| REP | 165 | 0.63 | 0.42; 0.84 * | 0.0001 |
| GLIB | 79 | 0.55 | 0.24; 0.86 * | 0.0005 |
| REP-GLIB | | 0.08 | -0.29; 0.45 | 0.6749 |
| REP | 267 | 0.58 | 0.41; 0.76 * | 0.0001 |
| GLIB | 133 | 0.45 | 0.21; 0.68 * | 0.0002 |
| REP-GLIB | | 0.14 | -0.13; 0.41 | 0.3123 |
| REP | 171 | 0.24 | 0.02; 0.46 * | 0.0298 |
| GLIP | 75 | 0.81 | 0.49; 1.14 * | 0.0001 |
| REP-GLIP | | -0.57 | -0.95; -0.19 * | 0.0036 |
| REP | 190 | 0.71 | 0.51; 0.92 * | 0.0001 |
| GLIC | 94 | 0.55 | 0.26; 0.84 * | 0.0002 |
| REP-GLIC | | 0.16 | -0.18; 0.50 | 0.3575 |

REP= Repaglinide, GLIB=Glibenclamide, GLIP=Glipzide, GLIC=Gliclazide. The statistics are obtained from an ANOVA with treatment and centre as fixed effects. An asterisk indicates statistical significance.

All three comparisons with glibenclamide showed similar changes with time in $HbA_{1c.}$ levels. Equivalence was also shown with gliclazide. Repaglinide appeared to be better than glipizide as indicated in the table 3. Analogous results were seen for fasting plasma glucose changes.

Subset analysis of all five comparator studies showed the greatest effect (a reduction of $HbA_{1c}$ of 1.5%) in patients previously treated with diet alone. In those who previously received oral hypoglycaemic agent monotherapy, glycaemic control was maintained. Those patients who had previously been treated with a combination therapy (sulphonyl urea and other hypoglycaemic agents) and were switched to monotherapy with repaglinide, had, as expected, an increase of 1% in $HbA_{1c}$.

The distribution of different dose levels was the same for repaglinide and the comparators with approximately 20% on dose level I (0.5 mg); 10-15% each on dose levels II and III (1 to 2 mg), and 50% on dose level IV (4 mg). Good $HbA_{1c} \leq 6.5\%$ or borderline $HbA_{1c} \leq 7.5\%$ control was achieved in 73% of the SU-naive patients while 43% achieved the same control in the previously SU-treated patients. Doses were titrated at the discretion of the investigator and given three times daily before meals. It was noted that some patients were not dosed optimally and should have received an increased dose.

Clinical studies in special population

There are no data in children or adolescents less than 18 years of age.

There is no clinical experience in treating patients with hepatic insufficiency or in patients with severe renal insufficiency.

About 25% (343) of the patients in the long-term active control trials were between 65 and 75 years of age but there were no patients above 75 years of age included in these clinical trials. As mentioned above, values for the pharmacokinetic parameters were comparable for elderly >65 years of age

although higher exposure of repaglinide was demonstrated in elderly patients with Type 2 diabetes versus healthy elderly. However, further analysis of the response in elderly showed that only few patients have managed to maintain adequate control when treated with a dose of 0.25 mg three times daily.

As described above exposure with repaglinide was increased in patients with severe renal impairment compared with healthy patients. The SPC reflects this issue. The clinical data base from the long-term studies included 257 elderly patients with mild/moderate (Creatinine clearance <80 ml/min) renal impairment.

**Clinical safety**

The total patient years of exposure corresponded to 1205 (repaglinide), 412 (glibenclamide), 74 (glipizide) and 89 (gliclazide). The data on repaglinide were obtained from about 1600 patients treated in the controlled trials and about 500 in the pharmacology trials. Overall 26% of the population were >65 years.

**Patient exposure**

Repaglinide exposure by demographic category in the adequate and well-controlled trials are shown in table 4.

Table 4

| | | Maximum Total Daily Dose of Repaglinide | | | | | |
|---|---|---|---|---|---|---|---|
| Demographic Category | Any Dose | 0.75 mg | 1.5 mg | 3 mg | 6 mg | 12 mg | 24 mg |
| Number of Subjects | 1563 | 34 (2%) | 294 (19%) | 209 (13%) | 191 (12%) | 812 (52%) | 23 (1%) |
| Sex | | | | | | | |
| Male | 995 (64%) | 27 (3%) | 189 (19%) | 146 (15%) | 123 (12%) | 493 (50%) | 17 (2%) |
| Female | 568 (36%) | 7 (1%) | 105 (18%) | 63 (11%) | 68 (12%) | 319 (56%) | 6 (1%) |
| Race | | | | | | | |
| Caucasian | 1388 (89%) | 28 (2%) | 260 (19%) | 186 (13%) | 169 (12%) | 724 (52%) | 21 (2%) |
| Black | 53 (3%) | 0 | 12 (23%) | 9 (17%) | 6 (11%) | 25 (47%) | 1 (2%) |
| Oriental | 17 (1%) | 0 | 3 (18%) | 2 (12%) | 1 (6%) | 11 (65%) | 0 |
| Other | 105 (7%) | 6 (6%) | 19 (18%) | 12 (11%) | 15 (14%) | 52 (50%) | 1 (1%) |
| Age | | | | | | | |
| ≤40 | 18 (1%) | 1 (6%) | 4 (22%) | 0 | 6 (33%) | 7 (39%) | 0 |
| 40-65 | 1146 (73%) | 29 (3%) | 209 (18%) | 159 (14%) | 132 (12%) | 600 (52%) | 17 (1%) |
| >65 | 399 (26%) | 4 (1%) | 81 (20%) | 50 (13%) | 53 (13%) | 205 (51%) | 6 (2%) |

Adverse events and serious adverse events/deaths

Treatment emergent adverse events

Treatment emergent adverse events (TEAEs) were defined as all adverse events which occurred after initiation of treatment until 7 days after ended treatment. As indicated in table 5, hypoglycaemia, upper respiratory tract infections, influenza-like symptoms, rhinitis, backpain, bronchitis, pain, headache and hyperglycaemia were reported in at least 5% of repaglinide patients. These events were generally mild and did not appear more frequently with repaglinide.

Table 5

USA and Europe Combined

| NN-ARD System-Organ Class/ | REP | | | GLIB | | | GLIP | | | GLIC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Preferred Term | n | (%) | E | n | (%) | E | n | (%) | E | n | (%) | E |
| Number exposed | 1228 | | | 417 | | | 81 | | | 99 | | |
| Body as a whole – General disorders | | | | | | | | | | | | |
| Influenza-like symptoms | 99 | 8% | 111 | 42 | 10% | 52 | 8 | 10% | 11 | 2 | 2% | 2 |
| Back pain | 75 | 6% | 99 | 30 | 7% | 35 | 4 | 5% | 4 | 3 | 3% | 3 |
| Pain | 67 | 5% | 80 | 31 | 7% | 41 | 3 | 4% | 4 | 1 | 1% | 1 |
| Headache | 61 | 5% | 113 | 23 | 6% | 79 | 4 | 5% | 5 | 2 | 2% | 2 |
| Respiratory system disorders | | | | | | | | | | | | |
| Upper resp tract infection | 126 | 10% | 169 | 50 | 12% | 68 | 3 | 4% | 3 | | | |
| Rhinitis | 90 | 7% | 113 | 27 | 6% | 33 | 12 | 15% | 14 | 9 | 9% | 9 |
| Bronchitis | 74 | 6% | 96 | 32 | 8% | 37 | 3 | 4% | 6 | 4 | 4% | 4 |
| Metabolic and nutritional disorders | | | | | | | | | | | | |
| Hypoglycaemia | 199 | 16% | 594 | 83 | 20% | 220 | 15 | 19% | 36 | 15 | 15% | 31 |
| Heperglycaemia | 61 | 5% | 67 | 22 | 5% | 24 | 5 | 6% | 6 | 3 | 3% | 3 |
| Gastro-intestinal system disorders | | | | | | | | | | | | |
| Abdominal pain | 56 | 5% | 61 | 21 | 5% | 23 | 2 | 2% | 2 | 5 | 5% | 5 |
| Diarrhoea | 54 | 4% | 63 | 25 | 6% | 42 | 5 | 6% | 6 | 1 | 1% | 1 |
| Musculo-skeletal system disorders | | | | | | | | | | | | |
| Arthralgia | 33 | 3% | 41 | 22 | 5% | 25 | | | | | | |
| Secondary terms | | | | | | | | | | | | |
| Injury accidental | 48 | 4% | 51 | 24 | 6% | 25 | 5 | 6% | 6 | 3 | 3% | 3 |

REP=Repaglinide, GLIB=Glibenclamide (USA: Glyburide), GLIP=Glipizide, GLIC=Gliclazide
n = number of patients
% = proportion of exposed patients having the event
E = number of adverse events

The withdrawal rates due to adverse events were comparable between the treatment groups as is indicated above in table 1. For repaglinide-treated patients, the primary reason for adverse event withdrawal were hyper- and hypoglycaemia and related symptoms.

Serious adverse events

The incidences of serious adverse events were similar between patients treated with repaglinide and sulfonylureas in the active control trials. Serious events accounted for less than 5% of the total number of events and were most frequently reported as myoendo, pericardial and valve disorders (primarily angina pectoris and myocardial infarction) but the incidences were not higher than would be expected in the general Type 2 diabetic population. However, in a sub group analysis an increased risk of cardio-vascular disorders were initially reported in repaglinide-treated patients compared with glibenclamide. The relative risk of serious cardiovascular adverse events ranged from 0.2 to 10.0 in various analysis with borderline statistical significance obtained in the analysis of all serious events combined (point estimate 2.2; 95%CI: 1.1-4.5). However, further assessment of data indicated that this

difference was due mainly to cases of angina pectoris of doubtful significance while there were no difference when looking at more severe manifestations of myocardial ischemia, for example myocardial infarction and cardiac deaths. Blinded re-reading of all ECGs from the glibenclamide-controlled and dose-tolerance trials showed changes in the ECG were consistent with what could be expected in a middle-aged diabetes population even with doses up to 20mg, 4 times daily. There were no ischaemic, arrhythmic or other changes (QTc prolongation) in the ECGs.

Thus, after statistical/epidemiological assessment of the data considering multiplicity testing and analysis of missing values and also taking into account the pooled study data with all sulfonyl ureas in the comparative trials and the background frequency in patients with Type 2 diabetes it was concluded that repaglinide did not pose any increased risk of cardiovascular events.

A long-term study recruiting approximately 6000 patients has been initiated by the applicant.

Deaths

There was no indication of excess mortality for repaglinide-treated patients compared to sulfonyl-urea-treated patients.

Laboratory findings

Hypoglycaemic reactions were reported in 16% of repaglinide-treated patients in the five active-controlled long-term trials. The majority of these reactions were graded as mild/moderate and were comparable to those seen in the control groups. Blood glucose measured in patients in connection with the occurrence of symptoms of hypoglycaemia suggested that relatively fewer cases occurred at very low blood glucose values (<45mg/dl) than in the sulfonylura-treated groups. The data supported that the risk of clinically significant hypoglycaemia was low both after treatment with repaglinide and during dose titration.

There did not seem to be any age dependency with regard to hypoglycaemic reactions albeit that there were no patients >75 years of age included in the clinical trials. As discussed under pharmacokinetics, the exposure was higher in elderly patients with Type 2 diabetes than in healthy elderly. The exact reason for this could not be determined.

It can presently not be ruled out that a higher exposure in elderly >75 years of age may pose a risk to these patients.

## 5. Overall conclusions and benefit/risk assessment

### Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physiochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated, and are controlled in a satisfactory way.

### Preclinical pharmacology and toxicology

Adequate pharmacodynamic and pharmacokinetic studies have been performed in rats and dogs.

Animal metabolism is similar to that in man. There was however, one metabolite in humans that could not be fully assessed pre-clinically because of low amounts being formed in animals. This metabolite identified as M10 is found in human urine and plasma at low concentrations (2% of administered dose). It was concluded that this low concentration is unlikely to represent a potential safety concern in humans.

### Efficacy

Doses and dose regimen have been sufficiently defined and adequate pharmacokinetic studies were performed with the limitations indicated in the relevant part of the SPC**.** *In vitro* studies show that the cytochrome P450 isoenzyme 3A4 is solely responsible for the oxidative metabolism of repaglinide. The involvement of CYP 3A4 in repaglinide biotrasformation was investigated in five clinical trials in healthy subjects. The results of these studies demonstrate that inducers, inhibitors or substrates of CYP 3A4 iso-enzymes do not influence the pharmacokinetics of repaglinide to a clinically relevant extent.

Also, the concomitant administration of repaglinide did not change the pharmakokinetics of ethinylestradiol and nifedipine, two compounds predominately metabolised by CYP 3A4. However there is some influence on the Cmax of simvastatin and rifampicin.Well defined clinical studies with active comparators and well defined study populations justify the claimed indication. It is concluded that repaglinide is at least equally effective as sulfonylureas in the treatment of NIDDM patients.

In the pharmacokinetic studies severe renal impairment led to an increased exposure of repaglinide. However, in the clinical long-term studies including 257 elderly patients with mild to moderate renal impairment, there were no indications of an increased incidence of hypoglycaemia in this patient group. Because of an increased sensitivity to insulin in patients with renal impairment, caution is advised in titrating these patients.

There is no clinical experience in treating patients with hepatic and severe renal insufficiency or in elderly >75 years of age or in children and adolescents <18 years of age.

The applicant will conduct post-marketing trials in special populations.

**Safety**

The clinical safety profile based on over 1600 patients treated with repaglinide was overall reassuring. The main reasons for withdrawal (13%) were hyperglycaemia (4%) and hypoglycaemia (1%).

The incidence of serious cardiovascular adverse events was higher with repaglinide than with glibenclamide, but the difference was mainly due to angina pectoris of doubtful clinical significance and was not present for more severe manifestations of myocardial ischemia such as infarction or death. Changes in ECG reflected those in a middle-aged diabetes population. After statistical/epidemiological assessment of the data considering multiplicity testing and analysis of missing values and also taking into account the pooled study data with all sulfonylureas in the comparative trials and the background frequency in patients with Type 2 diabetes it was concluded that repaglinide did not pose any increased risk of cardiovascular events.

Patients aged <65 year and those aged >65 years appeared to be similar with regard to withdrawal rates, dose levels attained/sustained and incidence of hypoglycaemia. As mentioned the company will perform further trials in elderly patients >75 years and in patients with renal impairment.

**Benefit/Risk Assessment**

There is a lack of clinical data in children and adolescents and in patients >75 years as well as in patients with hepatic and severe renal insufficiency. Pending comprehensive information on efficacy and safety in these patients groups the CPMP decided to highlight these concerns in the relevant sections of the SPC.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Prandin tablets in the treatment of Type 2 diabetes mellitus, was favourable in the following indication: "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".

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Prandin was favourable in the treatment of Type 2 diabetes.