SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Trazec. This scientific discussion has been updated until 1 February 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Trazec (nateglininde) is indicated for combination therapy with metformin of type 2 diabetes patients inadequately controlled despite a maximally tolerated dose of metformin alone. The daily dose is 60-180 mg daily.

Nateglinide is an aminoacid derivative of phenylalanine. Nateglinide is not structurally related to sulphonylureas. However, the mechanism of action is similar: nateglinide is an insulin secretagogue, decreasing blood glucose levels.

2. Chemical, pharmaceutical and biological aspects

Composition

Trazec film-coated tablets are available in 60 mg, 120 mg and 180 mg strengths containing nateglinide INN as the active substance. In addition to the active substance, the film-coated tablets contain standard excipients that are commonly used in solid oral dosage forms, chiefly lactose and microcrystalline cellulose. The remaining core ingredients are croscarmellose sodium, povidone and magnesium stearate.
The primary packaging consists of a thermoformed blister using rigid plastic films, PVC/PE/PVDC backed with a heat-sealable lacquered aluminium foil: thermolacquer/aluminium/external protective coating.

Active substance

Nateglinide is N-(trans-4-Isopropylcyclohexanecarbonyl)-D-phenylalanine, a chiral molecule which has no structural resemblance to other antidiabetic drugs.
It is manufactured by a third party and information was supplied in the form of an open and closed DMF. The process validation and investigation of potential critical parameters was satisfactory to assure a consistent good quality and purity of the active substance.

Proof of structure and chirality was demonstrated in the usual way with physicochemical and spectroscopic data. Two polymorphic forms are known, therefore, the most stable form was chosen for development of the finished product. The crystal form is confirmed using powder X-ray diffractiometry and infrared absorption spectrum. The X-ray diffraction method can detect the least stable form at the 5% level, which has no impact on bioavailability.

The specification includes tests for identity (IR, and powder X-ray diffraction), assay by HPLC (98-102 %), optical rotation, heavy metals, related substances by HPLC methods, loss on drying etc. Since nateglinide has a low solubility, particle size is also controlled by laser light diffraction and the specification limits have been validated with reference to human biostudies. In general, impurities are observed only at low levels and the limits proposed in the specification are justified with reference to animal toxicology studies.

Batch analytical data were provided on 50 batches of active substance in total, the majority of which were pilot scale batches used in safety and bioequivalence studies and clinical trials. Good uniformity and compliance with the specification was demonstrated.

Nateglinide has good stability characteristics that were demonstrated in a number of studies carried out on three pilot-scale batches stored under ICH conditions, including light stress. Real time studies at

25°C/60%RH were carried out over 48 months with accelerated studies carried out over 6 months. In summary the results support a 48-month retest period when stored at or below 30°C in polyethylene bags/fibre drums.

Other ingredients

All tablet core excipients comply with monographs in the Ph. Eur.
A declaration from the applicant confirmed that magnesium stearate and lactose monohydrate are manufactured in compliance with EU requirements concerning TSE.
The film-coat (coating premix) components meet the requirement of the Ph. Eur. except ferric oxide which complies with the French monograph. Premixes (red, pink and yellow for the three strengths) are tested according to the Novartis in-house monograph, which is acceptable.

Product development and finished product

Due to the low solubility of the active substance, product development has included investigations into particle size and polymorphism. However, since the most stable polymorph H is manufactured and assured by X-ray powder diffraction during testing of the active substance, polymorphism should not be a problem.
The impact of the particle size distribution of the nateglinide substance on drug product dissolution was investigated. Results from three ranges of particle size showed that the rate of dissolution is independent of particle size and therefore support the particle size specification as proposed by the manufacturer.

Excipients are standard ingredients in tablet formulation and used at typical range of concentration. The choice was based on compatibility studies results, where the drug substance showed excellent compatibility with all excipients including binary or ternary mixtures (storage at 50°C in dry and humid conditions for 2 months).
Bioequivalence studies were performed with the final formulation proposed for marketing to demonstrate equivalence to the pivotal clinical formulation.
Concerning bioequivalence between different strengths, a high degree of inter-subject variability was noted, which led to additional studies being performed with increased numbers of subjects using the 60 mg and 180 mg products. Results indicated satisfactory bioequivalence in terms of AUC and C_{max}.

The manufacturing process is uncomplicated but has been validated and is controlled by means of relevant in-process tests. Evidence of satisfactory GMP status has been presented for the intended site of manufacture for marketing.

The specification is comprehensive and includes tests for identity, assay dissolution, uniformity of content (Ph.Eur.) and impurities.

Stability of the Product

Stability studies were carried out on 7 pilot-scale batches of product at several sites of manufacture, including the site proposed for marketing, carried out under ICH conditions. Twelve-month data were available at the time of submission of the dossier. As may be expected from the stability profile of the active substance, very little degradation was observed during these studies, and no significant physical changes. A matrix program allowed for full testing of all batch/package/strengths at 12, 24 and 36 months. Since nateglinide tablets have been shown to be stable with minimal batch-to-batch variability, it is considered that data pooling from the matrix design gives satisfactory information for use in determining the shelf-life, in line with current CPMP/QWP guidance on this issue.

Results of these studies support the shelf-life as proposed in the SPC, i.e. 2 years when stored at or below 30°C in the original packing.

Discussion on chemical, pharmaceutical and biological aspects

Overall, the chemical and pharmaceutical information presented in this application dossier was detailed and well presented, and provided extensive validation in all relevant critical areas for both the

active substance and the finished product. Only very minor quality issues are not completely resolved at the time of the opinion, but these have no impact on the benefit/risk ratio and would not present a barrier to authorisation of the product.

3. Toxico-pharmacological aspects

Pharmacodynamics

The pharmacodynamic studies in animals are of good quality and compliance with GLP is satisfactory.

- *In vitro* studies

Receptor binding studies

Several *in-vitro* competitive binding/displacement studies demonstrated that the binding affinity of nateglinide was lower than that of glibenclamide and repaglinide for the sulphonylurea (SU) receptor. The SU receptor consists of a ligand-binding moiety (SUR1) and KIR 6.2. (an ATP-sensitive K+ channel). The interaction of a ligand with the SU receptor produces the depolarisation of the beta cell followed by a calcium influx into the beta cell through voltage-sensitive channels, with subsequent insulin release.

- *In vivo* studies

Electrophysiology and ion flux measurements

Results of patch-clamp studies of single rat pancreatic beta-cells showed that the effect of nateglinide is rapid and reversed upon removal of the compound. Nateglinide was less potent than repaglinide, glimepiride or glibenclamide whereas the potency of nateglinide was increased (3-fold) with increasing glucose levels.

The effects of nateglinide compared to repaglinide, glimepiride and glibenclamide on the membrane potential of rat pancreatic beta-cells were also studied in the presence of metabolic inhibitors. The IC_{50} value for closure of K^+ channels of nateglinide was over 400-fold lower in the presence of metabolic inhibitors;

Ion flux experiments showed that stimulation of the L-type Ca^{++} channel and inhibition of the delayed rectifier K_v K^+ channels were only observed at high doses with reduced magnitude of effects, thus direct effects are not thought to contribute to the overall response of nateglinide.

Insulin secretion/kinetics of insulin secretion

The effects of nateglinide on insulin release were confirmed from studies on isolated Langerhans islets and beta-cells lines and compared with other insulinotropic agents (repaglinide, glibenclamide and tolbutamide). Similar glucose sensitizing effects were also demonstrated in studies using rat pancreatic beta-cells; nateglinide left-shifted the glucose dose-response curve for insulin release and acted as a sensitizer of glucose-stimulated insulin secretion. No effect of nateglinide on glucagon secretion was observed at therapeutically relevant concentrations.

Kinetics of insulin release (*in-vitro* and *in-vivo* studies)

The kinetics of nateglinide on hormone secretion were studied using pancreas preparations, islets and in *in vivo* studies (Cynomolgus monkey). Nateglinide stimulated insulin release with a preferential effect on the early phase of insulin release while repaglinide and glipizide have a slower and longer insulinotropic effect.

In rat models of type 2 diabetes or in rats fed with a high fat diet (pre-meal dosing), gliclazide and nateglinide had similar initial efficacy followed by increase over time with nateglinide whereas it decreased with gliclazide. The pancreatic content of insulin was higher at the end of the study with nateglinide; nateglinide stimulated insulin release only during meals.

Selectivity of beta-cells versus cardiac and vascular K_{ATP+} channels

Nateglinide had higher selectivity on K^+_{ATP} channels of the pancreatic beta-cell compared to other hypoglycaemic agents (glibenclamide, repaglinide).

- General and safety pharmacology programme

General pharmacodynamic studies with nateglinide showed only non specific effects on blood pressure and gastrointestinal tract at high doses.

- Summary of salient findings

Pharmacodynamic activity of nateglinide has been demonstrated in respect of the proposed indication. Nateglinide appears to have a short-lived action on the early phase of insulin secretion.

Pharmacokinetics

Nateglinide is rapidly absorbed after oral administration in all species. The extent of absorption is independent of the dose or the frequency of dosing.

Comparisons of mouse, rat, rabbit, dog and human data showed that exposure in rodents was considerably lower than that in humans, whilst in dogs exposure was greater. Bioavailability in animals increased in a dose-dependent manner suggestive of saturable first-pass metabolism.
Multiple dosing resulted in increased exposure to radioactivity in rats and dogs.

Nateglinide was extensively bound to plasma proteins in all species. The potential for drug-drug interaction in relation to protein binding with nateglinide seems low as *in vitro* studies showed that the binding of nateglinide to plasma proteins was not affected by furosemide, propranolol, captopril, nicardipine, pravastatin, glibenclamide, warfarin, phenytoin, tolbutamide, or metformin; nateglinide did not affect protein binding of these compounds. High concentrations of salicylic acid and acetylsalicylic acid increased the free fraction of nateglinide. These concentrations may correspond to the anti-inflammatory doses used sometimes in rheumatology, however the increase in concentration of the free drug would result in an increase in clearance, with only small resulting effect on plasma glucose. After administration of radiolabelled nateglinide, radioactivity was distributed throughout the body. Organs showing tissue levels higher than that in blood were the liver, kidney, pancreas and mesenteric lymph nodes in the rat; and kidney, liver, heart and lung in the dog.
Nateglinide and its metabolites pass through the placenta. Concentrations in the uterus, ovaries, placenta, and mammary glands were 15-34% of plasma levels. The concentrations of radioactivity in fetal tissues and amniotic fluid were lower than that in the placenta. The exposure of the fetus was low, but sufficient for fetuses to be actually exposed in reproduction studies. Nateglinide is excreted in the milk of female rats; the milk to plasma ratio of $AUC_{0\text{-}48h}$ was 1.4.

All metabolites found in humans are also present in animal species used in the toxicology programme. The only pharmacologically active metabolite is M7 that is as potent as the parent compound. However, in view of the low levels in humans, M7 is not expected to contribute to the overall pharmacological activity *in vivo*.
In rats, biliary and renal excretion accounts for equal amounts of the dose whilst in dogs and mice biliary excretion predominates. The renal route is the principal route of excretion in humans.

The major metabolic pathway in humans is the oxidative metabolism of the isopropyl side chain, which is catalysed primarily by cytochrome (CYP) P450 isoform 2C9, with lesser involvement of CYP3A4. CYP2C9 is predicted to be 2- to 8-fold more active than CYP3A4 in nateglinide metabolism *in vivo*.

Toxicology

All toxicology studies were conducted in compliance with GLP regulations and appropriate guidelines.

- Single dose toxicity

Acute toxicity was assessed using oral route in rats and dogs, and i.v. injection in mice and dogs. Toxicity of nateglinide was low, but female rodents were more sensitive than males. In mice, the LD_{50}

was 200-400 mg/kg (iv); convulsions were observed at 400 mg/kg. In rats, the LD_{50} was > 2000 mg/kg with salivation, mumbling and decreased locomotor activity observed at high doses. In dogs (oral), vomiting was observed in the high-dose groups.

- Repeated dose toxicity

Repeated dose toxicity studies with a duration of up to 52 weeks were performed in mice, rats and dogs.

Occasional increases in liver enzymes were reported in rats and dogs at high doses with histopathological changes in the liver in the dog. These abnormalities were reversible and were attributed to extensive biliary excretion of nateglinide metabolites in the dog. The other target organ was the gastrointestinal tract (with mostly gastric erosions and ulcers) in rats and dogs. The safety ratio (AUC) for gastric ulcers was about 8.

- Reproduction studies

Studies were performed in rats and rabbits. There was no sign of teratogenesis in rats. Gall bladder agenesis and small gall bladders were observed in rabbit fetuses. A significant difference was observed between the group treated with the highest dose of nateglinide and the non treated group ($p<0.05$). Gallbladder agenesis was not considered as a spontaneous finding exacerbated by maternal toxicity in New Zealand White rabbits. The plasma / milk ratio was 1.4.
Nateglinide is contra-indicated during pregnancy and breast-feeding, and this has been mentioned in the SPC).

- Genotoxicity

Nateglinide was not genotoxic in the standard test battery.

- Carcinogenic potential

The carcinogenic potential of nateglinide was assessed using dietary administration to mice and rats in 2-year studies. In the first carcinogenicity study in rats, an increased incidence of benign pancreatic islet cell tumours was observed in females at the highest dose level. This was not confirmed in the second carcinogenicity study using 5-fold higher doses.
Nateglinide had no carcinogenic potential in mice. However, peripheral neuropathy was observed after 78 weeks in females mostly (up to 60 % of the females treated at intermediate and high doses levels).

Additional studies were performed to investigate the occurrence of peripheral neuropathy in mice, and the potential of nateglinide to stimulate beta cell division in the pancreas of rats.

The neuropathy lesions were characterised by axonal degeneration and Schwann cell proliferation; these lesions have been reported in untreated aged mice of this strain (B6C3F1). The safety ratio (AUC) for neuropathy was about 6. There was no increase in the incidence of neuropathy in nateglinide-treated mice in 5 additional studies (up to 78 weeks of treatment), nor in rats and dogs. Neuropathy was attributed to increase incidence of spontaneous lesions in aged mice treated at doses higher than the MTD.

Statistical analysis of pancreatic islet tumour incidence revealed a trend however, statistical significance was not attained in a pairwise comparison against controls. A study investigating potential excessive stimulation of the pancreas by nateglinide was performed at doses greater than those used in the carcinogenicity study; there was no increase in tumour incidence.

- Special toxicity studies

In rabbits, it was shown that nateglinide was not an ocular irritant. In addition, nateglinide did not produce haemolysis and is devoid of antigenic potential.

There was no evidence of potentially additive or synergistic toxic effects of nateglinide in combination with other hypoglycaemic agents (glibenclamide, glipizide and voglibose).
The toxicity of major metabolites was not found to differ from that of nateglinide.

- Impurities

The applicant has set appropriate limits for impurities.

- Environmental risk assessment

An environmental risk assessment has been performed and no effects from the therapeutic use of nateglinide are expected.

Discussion on toxico-pharmacological aspects

The ability of nateglinide to stimulate insulin release rapidly with a preferential effect on the early phase was demonstrated in rodents and a primate model of early type 2 diabetes (Cynomolgus monkey). It was shown that nateglinide acts via the sulphonylurea receptor but may differ from other agents mainly by the early onset and short effect duration.
General pharmacodynamic studies showed that nateglinide produces non-specific responses on blood pressure and the gastrointestinal tract at very high doses.

Nateglinide has low acute toxicity potential. In chronic toxicity studies, the target organs were the gastro-intestinal tract with gastric erosions and ulcerations, and the liver with occasional increases in enzymes in rats and dogs. A sufficient safety margin based on exposure was present in both cases.

In reproduction studies, there was no relevant effect of nateglinide on fertility, embryofetal development, parturition, lactation, and perinatal development in rats. In rabbits, at maternally toxic doses a higher incidence of foetuses with no gallblader was observed.

Nateglinide is not genotoxic. The mouse carcinogenicity study showed an increased incidence of peripheral neuropathy in females treated at doses exceeding the maximum tolerated dose. This was considered as spontaneous lesions occurring in this strain at toxic doses rather than a direct toxic effect. An increased incidence of benign pancreatic islet cell tumours was observed in male rats at high doses. The safety ratio for human use is considered acceptable thus the findings are not considered clinically relevant for the treatment of patients with type 2 diabetes.

4. Clinical aspects

Type 2 diabetes is a heterogeneous disease characterised by increased peripheral insulin resistance and abnormal insulin secretion. It has been suggested though not yet confirmed that agents e.g., glucose, amino acids, gastrointestinal peptides, and sulphonylureas share a final common mechanism. This is characterised by a reduction of negative cell potential leading to changes in calcium flux and triggering exocytosis. This was the basis for developing nateglinide, an amino acid derivative.

Other pharmacological agents for type 2 diabetes act by improving glucose sensitivity (e.g., metformin), reducing glucose uptake (acarbose), improving insulin secretion (sulphonylureas, repaglinide), or insulin substitution (exogenous insulin).

Nateglinide has been studied in 41 clinical pharmacology studies in over 800 subjects and patients, and in 12 double-blind controlled clinical trials in over 3000 patients.

Clinical pharmacology

Clinical pharmacology studies have been carried out in healthy volunteers, renal and hepatic patients and in type 2 diabetic patients.

Pharmacodynamics

- Mechanism of action

No clinical studies of the cellular mechanism of action were performed in addition to the preclinical studies.

- Dynamic studies

Nateglinide increased plasma insulin concentrations and decreased mealtime plasma glucose concentrations in a dose-dependent manner. In type 2 diabetic patients, nateglinide in oral doses of 30 to 240 mg administered 10 min before meals induced a rapid insulin response (35 min); the maximum decrease was seen for the 120-mg dose.
When compared to glibenclamide and repaglinide, the insulinotropic effect of nateglinide was characterised by a more rapid onset of action and a shorter duration of action. Nateglinide at 120 mg dose significantly decreased the 2-h incremental glucose compared to placebo and glibenclamide.
In the event of a missed meal, glucose nadirs were significantly lower in the glibenclamide than in the nateglinide treatment group. Moreover, hyperinsulinaemia was more prolonged (4 h to 8 h post-dose) after treatment with glibenclamide compared to nateglinide and placebo treatments (1 to 4 h).
The combination with metformin produced significant reductions in prandial plasma glucose excursions than either drug alone; the enhanced effects are likely due to a combination of increased insulin levels and improvement of peripheral insulin sensitivity.
Pharmacodynamic effects were similar in diabetic patients to those of healthy volunteers.
Primary and secondary pharmacodynamics have been well investigated.

Pharmacokinetics

The pharmacokinetics of nateglinide were investigated in healthy volunteers, type 2 diabetic patients and patients with impaired renal and liver function. Nateglinide was administered as tablets of 60 mg to 180 mg strength, or as a solution for intravenous injection in some studies. One study was performed with ^{14}C-labelled nateglinide.

Plasma concentrations of nateglinide were mainly determined using HPLC method with UV detection. The analytical method has been adequately validated and showed satisfactory accuracy and precision. The limit of quantification was 50 ng/ml (or lower); the interassay variability was < 10%.

- Absorption

No differences in pharmacokinetic parameters were observed between healthy volunteers and type 2 diabetic patients. Nateglinide exhibited a constant absorption rate over the dose range of 30 to 120 mg. Nateglinide mean AUC and Cmax increased linearly with dose and no accumulation after repeated dosing was observed.

Table 1. AUC and Cmax of various doses of nateglinide (given three times daily)

	30 mg	60 mg	120 mg	180 mg
AUC (µg.h/ml)	2.5 ± 1.2	4.4 ±+ 2.1	8.9 ± 5.0	14.1 ± 7.1
C_{max} (µg/ml)	1.4 ± 1.0	2.4 ± 1.4	4.6 ± 2.8	6.7 ± 3.6

After administration of an oral dose of 120 mg and an i.v. dose of 60 mg in 10 mn the absolute availability was about 75 % indicating a modest first-pass effect.

Influence of food

The pharmacokinetics of nateglinide were studied in healthy volunteers with respect to effect of food, meal composition, meal timing, gastric emptying, and in type 2 diabetics, effect of food, and missed meals.

These results indicated that nateglinide should be administered before meals because of lower C_{max} and T_{max} when given immediately after food. This is reflected in the SPC. Meal composition did not affect the pharmacokinetic parameters of nateglinide.

- Distribution

The Vd of nateglinide was about 10.5 l. Nateglinide is highly bound to plasma proteins (98%), mainly to serum albumin. The protein binding of the metabolites was not studied.

- Elimination

Nateglinide is extensively eliminated by metabolism by the mixed-function oxidase system (CYP 2C9 and 3A4). The main metabolites (M1, M2, and M3) result from hydroxylation of the isopropyl side-chain, either on the methyl carbon (M1), or one of the methyl groups (M2, M3). The main metabolites are about 5-6 and 3 times less potent than nateglinide, except for minor metabolite M7. Total clearance was 7.36 l/h and elimination half-life was 1.3 hour. The pharmacokinetics of the metabolites have not been studied. The relative systemic exposure of metabolites to parent drug was 9% for M1 and 3-4% for other. Urinary excretion is the primary elimination route of nateglinide, as unchanged drug for about 16%. Significant tubular secretion is likely assuming the absence of any passive tubular reabsorption. Only 10% of radiolabelled nateglinide dose was recovered in the faeces.

- Interaction studies

Medicinal products that are commonly used in type 2 diabetic patients have been evaluated and relevant doses were used in all interaction studies. Drug-drug interactions via metabolic induction or inhibition of the cytochrome P-450 enzymes (in particular CYP2C9) may be expected with nateglinide. As the enzymes involved in the metabolism of nateglinide have not been completely characterised, there is a risk for increased exposure to nateglinide during concomitant medication with inhibitors of cytochrome P450, especially CYP2C9 inhibitors. This could result in a more prolonged effect and possibly increased risk of hypoglycaemia. This has been mentioned in the SPC.
No interactions were demonstrated when nateglinide was concomitantly administered with diclofenac (CYP2C9), warfarin (CYP 2C9 and 3A4), digoxin, troglitazone (CYP 3A4 inducer), metformin and glibenclamide. No study was performed with oral contraceptives.

- Special populations

Renal impairment
A study was performed in patients with moderate to severe renal impairment (CrCL: 15-50 ml/min/1.73m²) receiving 120 mg. In moderate/severe renal impairment patients, the mean pharmacokinetic parameters of nateglinide were comparable to those of healthy subjects; in type 1 or 2 diabetic subjects on haemodialysis (when compared to healthy controls) the mean C_{max} decreased by 49 % , which is considered clinically relevant and could result in a loss of efficacy.

In patients with severe renal insufficiency, dose adjustment may be necessary as recommended in the SPC.

Hepatic impairment
The pharmacokinetics of 120 mg nateglinide were studied in patients with mild to moderate liver dysfunction (Child-Pugh classification 5-11) compared to healthy volunteers; nateglinide plasma AUC increased by 30% and Cmax by 37%. Severe hepatic impairment is a contraindication to the use of nateglinide.

Elderly
No pharmacokinetic study was performed in elderly.

Children
The pharmacokinetics of nateglinide have not been studied in children. This is acceptable as type 2 diabetes in children is rare.

Other populations
No specific studies were performed as regards gender, or race. A kinetic population analysis did not indicate the need for dose adjustment according to the BMI, race or gender.

- Bioequivalence studies:

Six studies were carried out under fasting conditions and the results showed that the tablets used in clinical trials were bioequivalent to those intended for marketing.

Clinical efficacy

The clinical trials were performed according to GCP standards and agreed international ethical principles.

Dose-response studies and main clinical studies

Dose response studies

The results of phase I studies led to the selection of a 30-180 mg dose range. Study P116 was a double-blind, placebo-controlled, crossover study. It showed that the 60-mg and 120-mg doses were more effective than the 30 mg, and both were similarly effective when administered three times daily, before meals.
Two trials were performed to establish the effective doses of nateglinide. Study B202 was a 12-week randomised, double blind, placebo-controlled, fixed-dose, parallel-group comparison of the efficacy and safety of four fixed doses of nateglinide in 289 patients (HbA_{1c} and FPG were the primary efficacy parameters). Study B302 was carried out in 697 patients (HbA_{1c} was the primary efficacy parameter).

In studies B 202 and B302, both HbA_{1c} and FPG decreased in the nateglinide 60 to 180 mg dose groups compared to baseline values. A linear dose response relationship was observed with nateglinide. Statistically significant reductions in HbA_{1c} (%) were obtained for the 120 and 180 mg doses only of about 0.6 and 0.7, respectively.
Changes in FPG (mmol/l) were observed with a maximum decrease of 1.0 for the 120 mg dose. The 180-mg dose was associated with further reductions in HbA_{1c} and FPG in study B302, but not in study B202.

The proposed doses of 60-180 mg are justified as the maximal effect on HbA_{1c} and plasma glucose was observed with these doses. However, the initial dose in combination with metformin should be 60 mg as the effect is additive and hypoglycaemia has been observed when patients were randomised to a 120-mg dose. The rationale for three times daily administration is based on pharmacodynamic results showing that nateglinide increases insulin release after meals. The 180-mg dose did not provide significant improvement in glycaemic control compared to 120 mg, however there might be a benefit for some patients after titration in clinical practice.

Main studies

1. Description of the studies

Table 2. Summary of main clinical trials

Study	Objectives	N	Entry criteria	Duration	Treatment	Population
Main clinical trials in type 2 diabetes patients						
B202	Dose-ranging DB, R, PG	289	HbA_{1c} 6.8-10.5% after diet and exercise for ≥ 3 months	12 weeks	Nat 30 mg, 60 mg, 120 mg or 180 mg, placebo	Diet-treated diabetics
B302	Dose-finding DB, R, PG	697	HbA_{1c} 6.8-11% after diet and exercise for ≥ 3 months	24 weeks	Nat 60, 120 & 180 mg or placebo	Diet-treated diabetics
B351	Comparison with Met alone or in combination DB, R, PG	701	HbA_{1c} 6.8-11% after diet and exercise for ≥ 3 months	24 weeks	Nat 120 mg, Met 3x500 mg, Nat 120 + Met 3x500 mg, placebo	Diet-treated diabetics
B354	Combination with Met DB, R, PG	467	HbA_{1c} 6.8-11% after 4 weeks therapy with met. ≥ 1500 mg	24 weeks	Met 2 g alone or with Nat 60 mg or Nat 120 mg	Diabetics on Met 2x1000 mg
B252	Combination with Met DB, R, PG	123		12 weeks	Met 3x500 mg alone or with Nat 60 mg or 120 mg	Diabetics on Met 3x500mg & SUs
B355	Comparison with Glib DB, R, PG	152	HbA_{1c} 6.8-11% after diet and exercise for ≥ 3 months	8 weeks	Nat 120 mg, Glib 10 mg o.d.	Diet-treated diabetics
B304	Comparison with Glib (switch) in SU treated patients DB, R	563		24 weeks	Nat 60 mg or 120 mg, Glib 10 mg	Diabetics on glibenclamide 10 mg o.d.
B251	Combination with Glib in Glib-treated patients DB, R, PG	172		12 weeks	Glib 10 mg alone or with Nat 60 mg or 120 mg	Diabetics on glibenclamide 10 mg o.d.
B356	Comparison with troglitazone alone or in combination DB, R, PG	599	HbA_{1c} 6.8-11% after diet and exercise for ≥ 3 months	16-24 weeks	Nat 120 mg, Trog 600mg, Nat 120mg + Trog 600mg, placebo	Diet-treated diabetics

Long term clinical trials						
B351E	Efficacy, safety and tolerability Nat or Nat +Met	400		26 weeks	120 mg, placebo replaced by Nateglinide 120 mg	Completers of B351
B202E	Safety and tolerability	227		40 weeks	30 mg, 60 mg, 120 mg &180 mg with or without Met	Completers of B202
B251E-01	Safety and tolerability Gli or Gli + nat	92	HbA_{1c} > 10% or inc > 1.5 % after completion of core	40 weeks	Glib 10 mg alone or with Nat 60 or 120mg	Completers of B251

Active comparators were accepted reference agents such as metformin and troglitazone. However, the comparison with troglitazone is of little support because troglitazone is not marketed in Europe and has been withdrawn from the market in the US due to hepatic toxicity. There was no comparison with sulphonylureas such as gliclazide and glipizide, nor with repaglinide; the combination of nateglinide and alpha-glucosidase inhibitors was not studied.

1. Primary endpoints

For all Phase III trials except B355 the primary efficacy endpoint was HbA_{1c}. In some trials, FPG was considered as a co-primary endpoint. Baseline was the average of the last 2 measurements from the run-in period. Responders were defined as patients having a reduction of HbA_{1c} > 10% from baseline. In B355 the primary endpoint was post-prandial glucose excursion.

Secondary efficacy endpoints included FPG, fasting insulin, post-prandial glucose (except B355), post-prandial insulin, C-peptide, lipids (i.e., total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, and triglycerides).
Fructosamine, an estimate of mean glycaemia over the past 2-3 weeks was measured in B202, B302 and B355.

2. Statistical analysis

The primary analysis of efficacy considered the intent-to-treat (ITT) population including all randomised patients who had at least one valid observation for an efficacy variable. The significance level was 5%. The primary efficacy analysis used the last observation carried forward (LOCF) approach for those patients who did not complete the final week efficacy assessment. An ANCOVA model including effects for treatment, centre, baseline HbA_{1c}, treatment by centre interaction, and treatment by baseline HbA_{1c} interaction was fitted.
Secondary efficacy variables considered the ITT population using a similar model as specified for the primary analysis model, and LOCF approach.
In studies 201, 251 and 252, sample size calculations were based on a clinically relevant difference of 1 unit in HbA_{1c} (a standard deviation of 1.5 absolute units), 5 % type 1 error, and 80 % power. In other studies, the standard deviation was 1.3 with other similar criteria.

3. Study populations/accountability of patients

Diabetic patients included had a mean baseline HbA_{1c} ranging from 7.98% – 8.48%. Patients included were of above 65 years of age (30.3 %), 5.6 % were over 75 years; the mean weight was 84.7 kg and the mean BMI, 29.1 kg/m².
Patients were treated by diet (65 %) and oral hypoglycaemic agents (19.5 % with glibenclamide and 16 % with metformin), without satisfactory glycaemic control.

4. Efficacy results

Monotherapy studies

- Efficacy of nateglinide versus placebo

Four placebo-controlled trials B202, B302, B351 and B356 have been carried out. All patients in these studies inadequately controlled by diet and exercise. However, 29-46% of patients were on oral hypoglycaemic agents (OHA) 2 months prior to randomisation . In two of these trials, the efficacy of nateglinide 120 mg in combination with metformin (B351) or troglitazone (B356) was also studied.
In study B 351, the mean HbA_{1c} concentration at baseline ranged from 8.27% to 8.43 %, and in study B356 from 8.1% to 8.4%.

Table 3. Changes in HbA_{1c} (%) values (B202, B302, B351, B356)

Treatment group	Study	N	Adjusted mean change from baseline	Difference from placebo	
					p-value
Placebo	202 (24 w)	58	0.07		
	302 (24 w)	168	0.15		
	351 (24 w)	160	0.45*		
	356 (16 w)	135	0.47*		
Nat 30mg	202	50	-0.2	-0.27	0.15
Nat 60mg	202	58	-0.38*	-0.45	0.01
	302	167	-0.35*	-0.51	<0.001**
Nat 120mg	202	62	-0.55*	-0.62	<0.001**
	302	167	-0.43*	-0.58	<0.001**
	351	171	-0.45*	-0.90	<0.001**
	356	144	-0.55*	-1.02	<0.001**
Nat 180mg	202	57	-0.56*	-0.64	<0.001**
	302	167	-0.58*	-0.73	<0.001**

*Statistically significantly change from baseline ($p<0.05$); ** Statistically significantly different from placebo

Table 4. Changes in FPG (µmol/l) values (B202, B302, B351 and B356)

Treatment group	Study	N	Adjusted mean change from baseline	Difference from placebo	
					p-value
Placebo	202 (24 w)	60	0.22		
	302 (24 w)	172	0.53*		
	351 (24 w)	165	0.37*		
	356 (16 w)	143	0.66*		
Nat 30mg	202	51	-0.42	-0.64	0.082
Nat 60mg	202	58	-0.46	-0.69	0.05
	302	171	-0.08	-0.61	0.004**
Nat 120mg	202	62	-0.92*	-1.14	0.001**
	302	168	-0.21	-0.74	<0.001**
	351	175	-0.72*	-1.09	<0.001**
	356	145	-0.54*	-1.20	<0.001**
Nat 180mg	202	57	-0.56*	-0.79	0.026
	302	170	-0.41*	-0.93	<0.001**

* Statistically significantly change from baseline ($p<0.05$); ** Statistically significantly different from placebo

Results showed a statistically significant ($p<0.05$) and dose-dependent decrease in HbA_{1c} and FPG at endpoint in the nateglinide groups compared to placebo; the reduction in HbA_{1c} ranged from –0.3 to –1%.

No significant effect related to BMI on the magnitude of the change in HbA_{1c} was observed.

- Analysis of responders

In study B302 responders were defined as the patients having a reduction of $HbA_{1c} \geq 10\%$ compared to baseline, and the number of patients having $HbA_{1c} \leq 8\%$ at week 24 with baseline > 8.5%. Results showed that 38% of patients on nateglinide had a reduction ≥ 10 % compared to 16 % on placebo; 46 % of patients on nateglinide had $HbA_{1c} \leq 8\%$ compared to 23 % on placebo.

Active comparator trials

Three trials were performed versus metformin (B351), glibenclamide (B355), and troglitazone (B356), respectively.

Table 5. Study B351, change in HbA_{1c} (%, ITT population)

Treatment	N	Adjusted mean change in HbA_{1c} (%) ± SE	95% CI	P value
placebo	160	+ 0.45 ± 0.09	(0.27, 0.62)	0.0001*
Nateglinide 120 mg tid	171	- 0.45 ± 0.09	(-0.62, -0.28)	0.0001*
Metformin 500 mg tid	172	- 0.78 ± 0.09	(-0.95, -0.61)	0.0001*
Nateglinide + metformin	162	- 1.43 ± 0.09	(-1.60, -1.25)	0.0001*
Nat 120 mg vs placebo	--	-0.9 ± 0.12	(-1.14 - -0.66)	0.0001*
Met 500 mg vs placebo	--	-1.23 ± 0.12	-1.48, -0.99)	0.0001*
Nat 120 mg vs Met 500 mg		+ 0.34 ± 0.12	(0.10, 0.57)	0.0061*

* statistically significant change from baseline ($p<0.05$)

Metformin monotherapy) produced greater reductions in HbA_{1c} and in FPG than nateglinide although a submaximal dose of metformin 500 mg tid (metformin can be titrated up to 2000-2500 mg/day) was used.

Study B355 used forced titration and comparison with glibenclamide using Sustacal challenge. Post prandial glucose excursion (PPGE) was calculated as the area under the pre-prandial and post-Sustacal plasma glucose-time curve between 0 and 4 hours ($AUC_{0\text{-}4\,h}$).
Nateglinide (120 mg) was significantly more effective than glibenclamide (5/10 mg once daily) or placebo in decreasing PPGE, but less effective than glibenclamide of FPG; however, HbA_{1c} was not measured in this study. No study was performed with other sulphonylureas (e.g., glipizide, gliclazide) and no conclusion can be drawn on the efficacy of nateglinide compared to a sulphonylurea.
The reduction in HbA_{1c} was less with nateglinide 120 mg tid than with troglitazone after 16 weeks of treatment, but the difference was not statistically significant (–0.55 and –0.75, respectively).

No clinical trial was performed versus repaglinide but a comparative pharmacodynamic study showed that the insulinotropic effect of nateglinide had a more rapid onset and a shorter duration of action than that of repaglinide (0.5 and 2 mg).

- Switch from other oral anti-hyperglycaemic agents

Nateglinide monotherapy was studied after switching from glibenclamide in patients not adequately controlled by glibenclamide (10 mg /day, study B304), and from glibenclamide in patients previously treated with a metformin-glibenclamide combination (study B252).

It was concluded that patients inadequately controlled by glibenclamide 10 mg cannot be switched to nateglinide as glibenclamide was significantly more effective than nateglinide.

In a phase II study of patients previously treated with a metformin/glibenclamide combination, the switch from glibenclamide to placebo or nateglinide 60 mg, or nateglinide 120 mg led to a deterioration of glycaemic control in all treatment groups.

Overall, nateglinide was less effective than glibenclamide administered alone or in combination with metformin.

Efficacy in combination

The efficacy of nateglinide was studied in combination with metformin (B351, B354), with sulphonylureas (B251), and with troglitazone (B356).

Table 6. Combination with metformin : adjusted mean changes in HbA_{1c}.

(24 weeks)	N	Adjusted mean change in HbA_{1c} (%) ± SE	95% CI	P value
Nat. 120 mg tid + Metformin 500 mg tid	162	- 1.43 ± 0.09	(-1.60, -1.25)	0.0001*
Nateglinide 120 mg tid	171	- 0.45 ± 0.09	(-0.62, -0.28)	0.0001*
Metformin 500 mg tid	172	- 0.78 ± 0.09	(-0.95, -0.61)	0.0001*
Placebo	160	+ 0.45 ± 0.09	(0.27, 0.62)	0.0001*
Nat. 120 mg tid + Metformin 500 mg tid versus placebo		- 1.88 ± 0.12	(-2.12, 1.63)	0.0001*

The rationale of using the combination of nateglinide+metformin in patients previously treated with diet only was not justified. However, an add-on affect was observed on HbA_{1c}, FPG and PPGE.

Study B354 was performed in patients inadequately controlled by prior metformin monotherapy (1000 mg bid) and diet.

Table 7. HbA_{1c} adjusted (least square means) changes (ITT population)

Treatment group	Baseline mean (SE)	Adjusted mean change from baseline (SE)	Difference from metformin (95 % CI)	Raw P value
Placebo/Met 1000 mg bid	8.24 (0.09)	+ 0.01 (0.08)	--	
Nat 60 mg/Met 1000 mg bid	7.99 (0.09)	– 0.35 (0.08)	- 0.36 (-0.59,-0.13)	0.003*
Nat 120 mg/Met 1000 mg bid	8.16 (0.08)	– 0.58 (0.08)	- 0.59 (-0.82,-0.36)	< 0.001*

* statistically significant at the 0.05 level after Dunnet's adjustment for multiple comparisons

This study was correctly designed to assess the efficacy of nateglinide in combination with sufficient doses of metformin in patients inadequately controlled by metformin alone. The addition of nateglinide improved glycaemic control.

Combination with glibenclamide (B251)

Table 8. HbA_{1c} (%) values (ITT population)

	Placebo + glibenclamide 10 mg N=58	Nateglinide 60 mg + glibenclamide 10 mg N=55	Nateglinide 120 mg + glibenclamide 10 mg N=54
Least square mean	+ 0.29	+ 0.22	0.02
95 % CI	0.02-0.56	-0.05-0.49	-0.32-0.28
p value	0.0341**	0.1153	0.8866

In patients previously treated with glibenclamide, the addition of nateglinide did not significantly reduce HbA_{1c} levels.

Combination with troglitazone (B356)

Table 9. Combination with troglitazone (adjusted mean changes in HbA_{1c}).

16 weeks	N	Adjusted mean change in HbA_{1c}± SE	95% CI	p-value
Nat. 120 mg tid + troglitazone 600 mg	146	- 1.68 ± 0.09	(-1.87, -1.50)	<0.001*
Nateglinide 120 mg tid	144	- 0.55 ± 0.19	(-0.74, -0.36)	<0.001*
Troglitazone 600 mg	145	- 0.75 ± 0.19	(-0.95, -0.55)	<0.001*
Placebo	135	+ 0.47 ± 0.19	(0.28, 0.67)	<0.001*
Nateglinide vs troglitazone		+ 0.20 ± 0.14	(-0.07, 0.48)	0.149
Nat. 120 mg tid + troglitazone 600 mg versus placebo	--	- 2.16± 0.14	(-2.42, 1.89)	<0.001

* statistically significant change from baseline ($p<0.05$)

Combination with troglitazone had a synergistic effect on HbA_{1c}.

- Long-term efficacy

Three one-year extension trials were performed (B351E, B202E, B251E). A total of 719 patients were enrolled in these studies, with 301 patients exposed to nateglinide monotherapy, and 234 to nateglinide combination.

Table 10. Change in HbA_{1c} in completers for nateglinide alone or in combination (B351E,B202E and B251E).

	Baseline HbA_{1c}			Combination therapy		
				N	HbA_{1c} at endpoint	change from baseline (95% CI)
B351-E Nat. 120 mg	8.48 %			66		with metformin -1.3
B202-E Nat. 120 mg Nat. 180 mg	9.01 % 8.98 %			15 16	8.50 ± 1.18 8.54 ± 2.13	with metformin - 0.5 - 0.4
B251-E Nat. 60 mg Nat. 120 mg				14 17		with glibenclamide + 0.085 - 0.02

In combination with metformin, the additive effect was maintained over time. In combination with glibenclamide, nateglinide 60 or 120 mg plus glibenclamide (10 mg) did not produce clinical improvement in glycaemic control in type 2 diabetic patients inadequately controlled on glibenclamide alone.

Clinical studies in special populations

No clinical trial was performed in patients with impaired renal or hepatic function.
No specific clinical trial was performed in elderly. However, a total of 975 patients ≥ 65 years were included in the trials, 436 exposed to nateglinide monotherapy and 193 to the combination with metformin. Pooling of trials B302 and B351 showed that age did not affect efficacy of nateglinide.

No specific trials were performed in children or adolescents, or pregnant women. The absence of data in children or adolescents less than 18 years old is acceptable as type 2 diabetes is rare in this population.

Discussion on clinical efficacy

From dose-ranging trials, 60 mg appeared to be the minimal effective dose and 180 mg the maximal effective dose.

The methodology used in the clinical trials was appropriate. The ITT population include patients who all randomised patients with at least one post-baseline efficacy evaluation; this may have introduce a bias but fortunately the number of patients excluded before providing efficacy data was low and hence the bias is considered unimportant. Adjustment for multiple comparisons was used but as most comparisons made were significant, multiple comparison was not a problem and interpretation of raw p values is safe.
As monotherapy, nateglinide efficacy (60 to 180 mg tid) was significantly greater than placebo with evidence of dose response. The 120-mg dose of nateglinide was found to be superior to the 60 mg, but in one out of 2 studies, the 180-mg dose did not lead to greater reductions in HbA_{1c} compared to 120 mg. Nateglinide monotherapy decreased HbA_{1c} (%) by 0.45-1.02 after 16 or 24 weeks of treatment compared to placebo.
Nateglinide (120 mg tid) was clearly less effective than metformin 500 mg tid in patients treated by diet only.
Nateglinide appears to be more effective than glibenclamide although the comparison was only made on PPGE only and not on HbA_{1c}. No adequate study was performed comparing nateglinide with other SUs.
Nateglinide was not compared to repaglinide or an alpha-glucosidase inhibitor.
The glycaemic control of patients stabilised on SUs worsened when switched on nateglinide.
Overall, the efficacy of nateglinide as monotherapy was less than that of both reference products used as first line therapy in type 2 diabetes. Monotherapy results suggested loss of effect over time (especially on FPG, in study B302, 354 and extension B351) after initial improvement.

In combination in patients not adequately controlled on metformin monotherapy, the addition of nateglinide (60 mg or 120 mg tid) produced a significant decrease in HbA_{1c} compared to metformin monotherapy.
In patients previously treated with SUs, nateglinide (120 mg tid) combined with glibenclamide did not improve HbA_{1c}. The absence of additive effect may be expected as these two compounds share the same mechanism of action. In patients previously treated with a metformin and glibenclamide combination, the switch from glibenclamide to nateglinide 60 mg, or 120 mg led to a deterioration of glycaemic control in all treatment groups.
The combination of nateglinide (120 mg tid) with troglitazone resulted in a synergistic effect on HbA_{1c}. However, troglitazone is not marketed in Europe and has been withdrawn from the US market because of hepatic toxicity.
The combination of metformin and nateglinide has not been compared to the widely used combination of metformin and SU in patients not adequately controlled on metformin monotherapy. This was not requested by the CPMP in their scientific advice of April 1996.

Clinical safety

Patient exposure

The safety analysis was performed on a total of 3156 patients, including all patients randomised in clinical data available with safety assessment post baseline, as of 30 June 1999. This does not include the placebo-controlled study B356 and ongoing clinical trials.

Table 11. Distribution of patients in the studies

Placebo controlled	Total	Number of patients				
B202, B302, B351, B355	n = 1831	Nat. alone (30-180 mg) n = 973	Met. n = 178	Nat. + Met n = 172	Glib n = 50	Placebo n = 458
Active controlled						
B251, B252, B304, B354	n = 1325	Nat. alone (60/120 mg) n = 378	Nat. + Glib. n = 114	Nat. + Met n = 396	Met. n = 194	Glib n = 243

Long term B202E, B251E, B351E	n = 719	
PK/PD studies 38 studies	n = 763 subjects/ patients	

A total of 2122 patients were exposed to nateglinide, 1441 (67.9%) to nateglinide monotherapy, 640 (30.2%) to the combination with metformin and 114 (5.4 %) with glibenclamide. Most of the patients were exposed to the treatment up to 6 months; 789 were exposed for at least 6 months, 190 received nateglinide for 1 year, 113 patients (7.8%) nateglinide monotherapy; 55 nateglinide + metformin; 22 nateglinide + glibenclamide.
420 patients were exposed to 60 mg, 740 to 120 mg, 230 to 180 mg.
Among the 3352 patients exposed in the overall programme, 71 % were < 65 years of age, 29 % (974) were ≥ 65 years, and 179 (5%) were ≥ 75 years of age.

Adverse events and serious adverse event/deaths

The most common adverse events (AEs) in the nateglinide and nateglinide+metformin group (≥ 3 % of patients) are summarised in table 17.

Table 12. Adverse events in clinical trials (completed studies)

All completed studies	Nateglinide n (%)	Nat + Met n (%)	Metformin n (%)	Glibenclamide n (%)	Placebo n (%)
Patients evaluated	1441 (100)	640 (100)	406 (100)	293 (100)	458 (100)
Pat. with ≥ 1 event	914 (63.4)	418 (65.3)	275 (67.7)	177 (60.4)	283 (61.8)
Upper respiratory infection	152 (10.5)	66 (10.3)	43 (10.6)	27 (9.2)	37 (8.1)
Hypoglycemia	150 (10.4)	93 (14.5)	28 (6.9)	58 (19.8)	19 (4.1)
Headache	66 (4.6)	32 (5.0)	20 (4.9)	21 (7.2)	28 (6.1)
Fatigue	56 (3.9)	24 (3.8)	16 (3.9)	9 (3.1)	19 (4.1)
Dizziness	52 (3.6)	24 (3.8)	11 (2.7)	13 (4.4)	10 (2.2)
Nausea	49 (3.4)	20 (3.1)	22 (5.4)	7 (2.4)	19 (4.1)
Diarrhea	46 (3.2)	54 (8.4)	50 (12.3)	6 (2.0)	14 (3.1)
Abdominal pain	44 (3.1)	29 (4.5)	17 (4.2)	6 (2.0)	15 (3.3)
Dyspepsia	30 (2.1)	26 (4.1)	17 (4.2)	4 (1.4)	12 (2.6)

Source: Adverse event CRF database

The overall incidence of AEs was similar in all treatment groups. The commonest AEs wee hypoglycaemia, URI, headache, sinusitis, nausea, dizziness, fatigue, back pain, and abdominal pain. Diarrhoea was less frequent in the nateglinide+metformin than in the metformin group (8.4% and 12.3%, respectively). Following the preclinical findings in mice, a re-analysis of clinical data did not show any cause for concern as regards neuropathy.

Hypoglycaemic reactions

Hypoglycaemia (HG) was defined as follows:

- any event suggestive of hypoglycaemia regardless of blood or plasma glucose level;
- symptomatic events suggestive of hypoglycaemia and confirmed by a blood glucose < 2.8 mmol/l (or plasma glucose equivalent ≤ 3.3 mmol/l);
- asymptomatic hypoglycaemia with the same values for blood glucose in the absence of symptoms.
- a grade 3 or 4 symptomatic event [each event was rated according to severity on a clinical grading scale of 1 (mild), 2 (moderate), 3 (requiring assistance), to 4 (requiring hospitalisation)}.

Monotherapy
In completed clinical trials of the initial submission, symptoms of hypoglycaemia were reported in 10.4% of patients on nateglinide monotherapy, 14.5% on nateglinide+metformin combination, 6.9% on metformin monotherapy, 19.8% on glibenclamide monotherapy, and 4.1% on placebo.
The high incidence of hypoglycaemia in the glibenclamide group may have been related to the choice of this SU comparator. HG was considered as mild in nearly all patients. The only event classified as grade 3 was observed with a 30-mg dose. There was no grade-4 event. The incidence of confirmed HG was lower with nateglinide (2.4%) than with glibenclamide (7.2%). More episodes of hypoglycaemia were observed in patients randomised to 180 mg (17%) than to 120 mg (12.8%) or 60 mg (10.5%), but there was no increase in severity.

Combination therapy
The incidence of HG, but not the timing of the event, was dose-dependent. Most occurred with 120 mg in patients with low HbA_{1c} values at baseline. The risk of hypoglycaemia in patients whose baseline HbA_{1c} is close to therapeutic target is mentioned in the SPC.
When blood glucose was determined following the occurrence of symptoms of hypoglycaemia, slightly fewer nateglinide-treated patients had very low blood doses values (≤ 3,3 mmol/l) compared to the sulphonylurea-treated patients.

Cardiovascular safety
Diabetic patients are at increased risk for cardiovascular events and this was monitored in the 12 controlled clinical trials. In addition, vital signs and ECGs were monitored.
The incidence of myocardial infarction, angina pectoris and coronary artery disease was comparable in all treated groups. In view of the data provided, there is no evidence for cardiovascular concern with nateglinide.

Effect on body weight
Weight gain during long-term therapy was not significant in nateglinide monotherapy treated patients (B202-E) or in combination with metformin (B351-E) or glibenclamide (B251-E). In study B351-E, the mean weight gain after 52 weeks was +1.2 kg, +0.34 kg and –1.0 kg in the nateglinide, nateglinide+metformin, and metformin groups, respectively.

Deaths and serious adverse events

Table 13. Deaths and serious AEs in the double blind clinical trials (completed studies)

	Nateglinide	Nat. +Met.	Nat. + Glib	Metformin	Glibenclamide	Placebo
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total patients †	1448 (100)	640 (100)	114 (100)	406 (100)	293 (100)	459 (100)
AEs leading to discontinuation	78 (5.4)	46 (7.2)	9 (7.9)	29 (7.1)	11 (3.8)	28 (6.1)
Deaths	3 (0.2)	2 (0.3)	0	1 (0.2)	3 (1.0)	0
Total patients ‡	1441 (100)	640 (100)	114 (100)	406 (100)	293 (100)	458 (100)
SAEs	56 (3.9)	30 (4.7)	7 (6.1)	18 (4.4)	20 (6.8)	20 (4.4)

† Total patients randomised ; ‡ Total patients randomized with at least one post-baseline measurement

Deaths were reported in 9 patients; 3 received nateglinide as monotherapy and 2 nateglinide in combination with metformin. Three patients died post study: 1 was treated with placebo, 1 with nateglinide 120 mg and 1 with metformin 500 mg.
The majority of deaths were cardiovascular in nature: myocardial infarction (1 on nateglinide 30 mg, 3 on glibenclamide 10 mg and 1 post study (nateglinide 120 mg); cardiac arrest (1 on nateglinide 120 mg +metformin); tachycardia (1 on nateglinide 120 mg); sudden death (1 on nateglinide 60 mg +metformin); arteriosclerotic disease (1 patient on metformin 500 mg). The other causes of death were pancreas neoplasm malignant on metformin (1), hepatic failure on placebo (1), and car accident on nateglinide (1, it should be noted that the patient was not driving). None of the deaths was considered as related to treatment by the investigator and there is no indication of excess mortality for nateglinide-treated patients compared to other treated groups.

Serious adverse events

The most frequently reported SAEs were cardiovascular events such as angina pectoris and myocardial infarction, neurological and musculoskeletal disorders. There was no difference in the incidence of SAE in the nateglinide-treated patients compared to the other groups.

Discontinuation due to adverse events

The incidence of discontinuations for an AE in the nateglinide group was comparable to that of the placebo group (5.4% and 6.1% respectively). In all completed studies, the main reasons for nateglinide-treated patients to withdraw were fatigue (0.8%), and symptoms relating to hyperglycaemia (thirst (0.7%), polyuria (0.5%) and nocturia (0.3%)). Discontinuation for hypoglycaemia occurred in 0.3%. The most common AEs leading to discontinuation in the nateglinide plus metformin group were gastrointestinal (nausea, diarrhoea) and most likely attributable to metformin.

No patient had abnormal laboratory test as primary reason for discontinuation. However, in study B202, one patient treated with nateglinide 180 mg withdrew because of an increase in gamma-GT, AST and ALT and this was considered as possibly related to study drug by the investigator; a patient treated in combination with metformin had a change in gamma-GT, AST and ALT from day 187 to 371.

Laboratory findings

Adequate laboratory follow up has been performed in clinical trials.

Blood

A small number of patients in the nateglinide and nateglinide plus metformin treatment groups had decreases from baseline in haematocrit, however these anomalies were due to other causes (e.g., haemorrhaging ulcer).

Liver function tests

The proportion of patients meeting criteria for change in liver function tests (ALT, AST, Gamma-GT, alkaline phosphatases, and total bilirubin) was similar in the nateglinide, nateglinide + metformin and the placebo groups. Twelve patients (8 on nateglinide monotherapy and 4 on combination) had increases in liver function tests characterised by rises in ALT and/or AST (>3 ULN) by day 30-93; enzyme values returned to normal in spite of continuing therapy with nateglinide in most cases.

Lipids

Table 14 summarises the evolution of lipid profile in all clinical trials.

Table 14. Mean lipid changes from baseline according to treatment group.

Lipid changes	Nateglinide	Nateglinide + metformin	Metformin	Glibenclamide	Placebo
N of patients	1368	640	405	293	336
Mean change from baseline					
HDL (mmol/l)	0	0	0	0	0
LDH (U/l)	-3.1	-4.9	-0.6	-0.6	-2.5
LDL (mmol/l)	0	0	-0.1	-0.1	0
Total cholesterol (mmol/l)	0.1	0	0	0	0
Triglycerides (mmol/l)	0	-0.1	0.1	0	-0.1

There were no differences in lipids between treatment groups, however**,** overall increases in triglycerides and lipids were observed in about 10 % of all patients whatever the active treatment. Further analysis according to the baseline level of fasting lipids showed inconsistent effects of nateglinide.

Safety in special populations

With nateglinide (overall monotherapy and metformin combination groups) the incidence of hypoglycaemia was higher in patients ≥ 75 years (13.8%) than in patients < 65 years (10.6%). In patients ≥ 65 years treated with the nateglinide+metformin combination, the incidence of hypoglycaemia was higher (17.1%) than in patients < 65 years (13.4%)

Discussion on clinical safety

There is a sufficient safety database for nateglinide. Withdrawals for AEs were primarily due to fatigue, hypoglycaemia and symptoms relating to hyperglycaemia, especially when nateglinide was combined to metformin. There was no excess mortality for nateglinide-treated patients compared to placebo or other oral antihyperglycaemic agents.

The most common reported AEs in monotherapy were upper respiratory tract infection, hypoglycaemia, fatigue and headache.

Adequate monitoring of cardiac function was performed in nateglinide clinical trials. There was no cardiovascular safety concern raised with nateglinide. No concerns were identified as regards liver function tests in patients receiving nateglinide and no specific monitoring of liver function is recommended in the SPC. Inconsistent effects on lipids were observed.

In combination studies with metformin, more adverse events in the nateglinide 120-mg group were reported, especially hypoglycaemia in patient whose baseline HbA_{1c} was near therapeutic target. In these patients, the risk of hypoglycaemia has been mentioned in the SPC.
In combination with metformin, an increase in the incidence of hypoglycaemia was found in patients ≥ 65 years compared to younger patients. Due to additive effects of nateglinide and metformin, there is a risk of hypoglycaemia in patients receiving this combination, especially in elderly. For all patients, the recommended starting dose is 60 mg, this is included in the SPC.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

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

Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

Preclinical pharmacology and toxicology

The preclinical studies of nateglinide were of good quality.

The ability of nateglinide to stimulate insulin release rapidly with a preferential effect on the early phase was demonstrated. It was shown that nateglinide acts via the sulphonylurea receptor but may differ from other agents. No concern was identified in safety pharmacodynamic studies.

The pharmacokinetics of nateglinide were well investigated in relevant species. The Applicant has committed to study the role of CYP2C9 in the metabolism of nateglinide and the potential of CYP2C9 inhibitors to affect nateglinide pharmacokinetics *in vivo*.

Nateglinide has low acute toxicity potential. In chronic toxicity studies, the target organs were the gastro-intestinal tract with gastric erosions and ulcerations, and the liver with occasional increases in enzymes in rats and dogs. A sufficient safety ratio based on exposure (AUC) was present in both cases. Reproduction studies showed no relevant effect of nateglinide on fertility, embryofetal development, parturition, lactation, and perinatal development in rats. In rabbits, at maternally toxic doses a higher incidence of foetuses with no gallblader was observed.
Nateglinide is contra-indicated during pregnancy and breastfeeding.

Nateglinide was not genotoxic in the usual battery of tests. The mouse carcinogenicity study showed an increased incidence of peripheral neuropathy in females treated at doses exceeding the MTD. This was attributed to spontaneous lesions occurring in this strain at toxic doses rather than a direct toxic effect. An increased incidence of benign pancreatic islet cell tumours was observed in male rats at high doses, possibly due to hyperstimulation of insulin release by nateglinide. The findings were not considered as a concern for therapeutic use in type 2 diabetes as the safety ratio for human use was considered acceptable.

Efficacy

In clinical trials, the dose of 60 mg three times daily (before main meals) appeared to be the minimal effective dose and 180 mg the maximal effective dose.

As monotherapy, nateglinide efficacy on HbA_{1c} (60 to 180 mg three times daily, tid) was significantly greater than placebo with evidence of dose response. Nateglinide monotherapy decreased HbA_{1c} by 0.45-1.02% after 16-24 weeks of treatment.

However, the efficacy of nateglinide (120 mg tid) was less than that of a suboptimal dose of metformin (500 mg tid) in patients treated by diet only.

Nateglinide was more efficacious than glibenclamide on PPGE, but less efficacious than glibenclamide on the basis of trial using FPG; HbA_{1c} was not measured in this trial. No adequate study was performed comparing nateglinide with other SUs. The glycaemic control of patients stabilised on SUs and switched to nateglinide worsened on nateglinide. In addition, nateglinide was not compared to repaglinide or an alpha-glucosidase inhibitor.

Overall, the efficacy of nateglinide as monotherapy was less than that of reference oral antidiabetics and results suggested a loss of effect over time.

In patients not adequately controlled on metformin monotherapy, the addition of nateglinide (60 mg or 120 mg tid) to metformin produced a significant decrease in HbA_{1c} compared to metformin monotherapy.

In patients previously treated with SUs, nateglinide (120 mg tid) combined with glibenclamide did not improve HbA_{1c}. In patients previously treated with a metformin and glibenclamide combination, the switch from glibenclamide to nateglinide 60 mg, or 120 mg led to a deterioration of glycaemic control in all treatment groups. Nateglinide was also studied in combination with troglitazone, however, troglitazone is not marketed in Europe and has been withdrawn from the US market due to hepatic toxicity.

The combination of metformin and nateglinide has not been compared to the widely used combination of metformin and SU in patients not adequately controlled on metformin monotherapy. This was not requested by the CPMP in their scientific advice of April 1996. Some CPMP members considered that this information should be provided before the Marketing Authorisation, however the majority of the CPMP considered that this could be documented after granting the marketing authorisation. The Applicant has committed to document further the efficacy and safety of the combination of nateglinide plus metformin against a combination of metformin plus sulphonylurea.

Safety

A sufficient number of patients have been exposed to nateglinide in the safety database. Overall the safety profile was considered acceptable. Withdrawals for adverse events from clinical trials were due primarily to hypoglycaemia and related-symptoms, especially when nateglinide was combined to metformin. There is no excess mortality for nateglinide-treated patients compared to placebo or other oral antihyperglycaemic agents.

The most commonly reported adverse events in monotherapy were upper respiratory tract infection, hypoglycaemia, fatigue and headache. There was no cardiovascular safety concern raised with nateglinide. No concerns were identified as regards liver function tests in patients receiving nateglinide and no specific monitoring of liver function is recommended in the SPC. Inconsistent effects on lipids were observed.

In combination studies with metformin, more adverse events in the nateglinide 120-mg group were reported, especially hypoglycaemia in elderly, and in patients whose baseline HbA_{1c} was near therapeutic target.

Benefit/risk assessment

In combination therapy with metformin, nateglinide has demonstrated its efficacy and safety for the treatment of type 2 diabetes patients inadequately controlled despite a maximally tolerated dose of metformin alone.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the benefit to risk profile of Trazec as combination therapy with metformin for type 2 diabetes patients inadequately controlled despite a maximally tolerated dose of metformin alone was favourable, and therefore recommended the granting of the marketing authorisation.