ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRAZEC 60 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 60 mg nateglinide.

Excipients:
Lactose monohydrate: 141.5 mg per tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

60 mg pink, round, bevelled-edge tablets with "NVR" marked on one side and "TS" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nateglinide is indicated for combination therapy with metformin in type 2 diabetic patients inadequately controlled despite a maximally tolerated dose of metformin alone.

4.2 Posology and method of administration

Nateglinide should be taken within 1 to 30 minutes before meals (usually breakfast, lunch and dinner).

The dosage of nateglinide should be determined by the physician according to the patient's requirements.

The recommended starting dose is 60 mg three times daily before meals, particularly in patients who are near goal HbA_{1c}. This may be increased to 120 mg three times daily.

Dose adjustments should be based on periodic glycosylated haemoglobin (HbA_{1c}) measurements. Since the primary therapeutic effect of Trazec is to reduce mealtime glucose, (a contributor to HbA_{1c}), the therapeutic response to Trazec may also be monitored with 1–2 hour post-meal glucose.

The recommended maximum daily dose is 180 mg three times daily to be taken before the three main meals.

Specific patient groups
Elderly
The clinical experience in patients over 75 years of age is limited.

Children and adolescents
There are no data available on the use of nateglinide in patients under 18 years of age, and therefore its use in this age group is not recommended.

Patients with hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. As patients with severe liver disease were not studied, nateglinide is contraindicated in this group.

Patients with renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment. Although there is a 49% decrease in C_{max} of nateglinide in dialysis patients, the systemic availability and half-life in diabetic subjects with moderate to severe renal insufficiency (creatinine clearance 15–50 ml/min) was comparable between renal subjects requiring haemodialysis and healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

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

4.3 Contraindications

Trazec is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients
- Type 1 diabetes (insulin-dependent diabetes mellitus, C-peptide negative)
- Diabetic ketoacidosis, with or without coma
- Pregnancy and breast-feeding (see section 4.6)
- Severe hepatic impairment

4.4 Special warnings and precautions for use

General
Nateglinide should not be used in monotherapy.

Like other insulin secretagogues, nateglinide is capable of producing hypoglycaemia.

Hypoglycaemia has been observed in patients with type 2 diabetes on diet and exercise, and in those treated with oral antidiabetic agents (see section 4.8). Elderly, malnourished patients and those with adrenal or pituitary insufficiency or severe renal impairment are more susceptible to the glucose-lowering effect of these treatments. The risk of hypoglycaemia in type 2 diabetic patients may be increased by strenuous physical exercise, or ingestion of alcohol.

Symptoms of hypoglycaemia (unconfirmed by blood glucose levels) were observed in patients whose baseline HbA_{1c} was close to the therapeutic target (HbA_{1c} <7.5%).

Combination with metformin is associated with an increased risk of hypoglycaemia compared to monotherapy.

Hypoglycaemia may be difficult to recognise in subjects receiving beta blockers.

When a patient stabilised on any oral hypoglycaemic agent is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, it may be necessary to discontinue oral hypoglycaemic treatment and replace it with insulin on a temporary basis.

Trazec contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, of the Lapp lactase deficiency or of glucose-galactose malabsorption should not take this medicine.

Specific patient groups
Nateglinide should be used with caution in patients with moderate hepatic impairment.

No clinical studies have been conducted in patients with severe hepatic impairment or children and adolescents. Treatment is therefore not recommended in these patient groups.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products influence glucose metabolism and possible interactions should therefore be taken into account by the physician:

The following agents may enhance the hypoglycaemic effect of nateglinide: angiotensin-converting enzyme inhibitors (ACEI).

The following agents may reduce the hypoglycaemic effect of nateglinide: diuretics, corticosteroids, and beta2 agonists.

When these medicinal products are administered to or withdrawn from patients receiving nateglinide, the patient should be observed closely for changes in glycaemic control.

Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

In an interaction trial with sulfinpyrazone, a CYP2C9 inhibitor, a modest increase in nateglinide AUC (~28%) was observed in healthy volunteers, with no changes in the mean C_{max} and elimination half-life. A more prolonged effect and possibly a risk of hypoglycaemia cannot be excluded in patients when nateglinide is co-administered with CYP2C9 inhibitors.

Particular caution is recommended when nateglinide is co-administered with other more potent inhibitors of CYP2C9, e.g. fluconazole or gemfibrozil, or in patients known to be poor metabolisers for CYP2C9.

Interaction studies with a 3A4 inhibitor have not been carried out *in vivo.*

In vivo, nateglinide has no clinically relevant effect on the pharmacokinetics of medicinal products metabolised by CYP2C9 and CYP3A4. The pharmacokinetics of warfarin (a substrate for CYP3A4 and CYP2C9), diclofenac (a substrate for CYP2C9), and digoxin were unaffected by coadministration with nateglinide. Conversely, these medicinal products had no effect on the pharmacokinetics of nateglinide. Thus, no dosage adjustment is required for digoxin, warfarin or other drugs that are CYP2C9 or CYP3A4 substrates upon coadministration with Trazec. Similarly, there was no clinically significant pharmacokinetic interaction of Trazec with other oral antidiabetic agents such as metformin or glibenclamide.

Nateglinide has shown a low potential for protein displacement in *in vitro* studies.

4.6 Pregnancy and lactation

Studies in animals have shown developmental toxicity (see section 5.3).

There is no experience in pregnant women, therefore the safety of Trazec in pregnant women cannot be assessed. Trazec, like other oral antidiabetic agents, is not recommended for use in pregnancy.

Nateglinide is excreted in the milk following a peroral dose to lactating rats. Although it is not known whether nateglinide is excreted in human milk, the potential for hypoglycaemia in breast-fed infants may exist and therefore nateglinide should not be used in lactating women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Based on the experience with nateglinide and with other hypoglycaemic agents, the following adverse reactions have been seen. Frequencies are defined as: common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000).

Hypoglycaemia
As with other antidiabetic agents, symptoms suggestive of hypoglycaemia have been observed after administration of nateglinide. These symptoms included sweating, trembling, dizziness, increased appetite, palpitations, nausea, fatigue, and weakness. These were generally mild in nature and easily handled by intake of carbohydrates when necessary. In completed clinical trials, symptoms of hypoglycaemia were reported in 10.4% with nateglinide monotherapy, 14.5% with nateglinide+metformin combination, 6.9% with metformin alone, 19.8% with glibenclamide alone, and 4.1% with placebo.

Immune system disorders
Rare: Hypersensitivity reactions such as rash, itching and urticaria.

Metabolism and nutrition disorders
Common: Symptoms suggestive of hypoglycaemia.

Gatrointestinal disorders
Common: Abdominal pain, diarrhoea, dyspepsia, nausea.
Uncommon: Vomiting.

Hepatobiliary disorders
Rare: Elevations in liver enzymes.

Other events
Other adverse events observed in clinical studies were of a similar incidence in Trazec-treated and placebo-treated patients.

Post-marketing data revealed very rare cases of erythema multiforme.

4.9 Overdose

In a clinical study in patients, Trazec was administered in increasing doses up to 720 mg a day for 7 days and was well tolerated. There is no experience of an overdose of Trazec in clinical trials. However, an overdose may result in an exaggerated glucose-lowering effect, with the development of hypoglycaemic symptoms. Hypoglycaemic symptoms without loss of consciousness or neurological findings should be treated with oral glucose and adjustments in dosage and/or meal patterns. Severe hypoglycaemic reactions with coma, seizure or other neurological symptoms should be treated with intravenous glucose. As nateglinide is highly protein-bound, dialysis is not an efficient means of removing it from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: D-phenylalanine derivative, ATC code: A10 BX 03

Nateglinide is an amino acid (phenylalanine) derivative, which is chemically and pharmacologically distinct from other antidiabetic agents. Nateglinide is a rapid, short-acting oral insulin secretagogue. Its effect is dependent on functioning beta cells in the pancreas islets.

Early insulin secretion is a mechanism for the maintenance of normal glycaemic control. Nateglinide,

when taken before a meal, restores early or first phase insulin secretion, which is lost in patients with type 2 diabetes, resulting in a reduction in post-meal glucose and HbA_{1c}.

Nateglinide closes ATP-dependent potassium channels in the beta-cell membrane with characteristics that distinguish it from other sulphonylurea receptor ligands. This depolarises the beta cell and leads to an opening of the calcium channels. The resulting calcium influx enhances insulin secretion. Electrophysiological studies demonstrate that nateglinide has 45–300-fold selectivity for pancreatic beta cell versus cardiovascular K^+_{ATP} channels.

In type 2 diabetic patients, the insulinotropic response to a meal occurs within the first 15 minutes following an oral dose of nateglinide. This results in a blood-glucose-lowering effect throughout the meal period. Insulin levels return to baseline within 3 to 4 hours, reducing post-meal hyperinsulinaemia.

Nateglinide-induced insulin secretion by pancreatic beta cells is glucose-sensitive, such that less insulin is secreted as glucose levels fall. Conversely, the coadministration of food or a glucose infusion results in an enhancement of insulin secretion.

In combination with metformin, which mainly affected fasting plasma glucose, the effect of nateglinide on HbA_{1c} was additive compared to either agent alone.

Nateglinide efficacy was inferior to that of metformin in monotherapy (decrease in HbA_{1c} (%) with metformin 500 mg three times daily monotherapy: –1.23 [95% CI: –1.48; –0.99] and with nateglinide 120 mg three times daily monotherapy –0.90 [95% CI: –1.14; –0.66]).

The efficacy of nateglinide in combination with metformin has been compared to the combination of gliclazide plus metformin in a 6-month randomised, double-blind trial in 262 patients using a superiority design. The decrease from baseline in HbA_{1c} was –0.41% in the nateglinide plus metformin group and –0.57% in the gliclazide plus metformin group (difference 0.17%, [95% CI –0.03, 0.36]). Both treatments were well tolerated.

An outcome study has not been conducted with nateglinide, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated.

5.2 Pharmacokinetic properties

Absorption and bioavailability

Nateglinide is rapidly absorbed following oral administration of Trazec tablets prior to a meal, with mean peak drug concentration generally occurring in less than 1 hour. Nateglinide is rapidly and almost completely (≥ 90%) absorbed from an oral solution. Absolute oral bioavailability is estimated to be 72%. In type 2 diabetic patients given Trazec over the dose range 60 to 240 mg before three meals per day for one week, nateglinide showed linear pharmacokinetics for both AUC and C_{max}, and t_{max} was independent of dose.

Distribution

The steady-state volume of distribution of nateglinide based on intravenous data is estimated to be approximately 10 litres. *In vitro* studies show that nateglinide is extensively bound (97–99%) to serum proteins, mainly serum albumin and to a lesser extent $alpha_1$-acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1–10 μg Trazec/ml.

Metabolism

Nateglinide is extensively metabolised. The main metabolites found in humans result from hydroxylation of the isopropyl side-chain, either on the methine carbon, or one of the methyl groups; activity of the main metabolites is about 5–6 and 3 times less potent than nateglinide, respectively. Minor metabolites identified were a diol, an isopropene and acyl glucuronide(s) of nateglinide; only the isopropene minor metabolite possesses activity, which is almost as potent as nateglinide. Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly

metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

Excretion
Nateglinide and its metabolites are rapidly and completely eliminated. Most of the [14C] nateglinide is excreted in the urine (83%), with an additional 10% eliminated in the faeces. Approximately 75% of the administered [^{14}C] nateglinide is recovered in the urine within six hours post-dose. Approximately 6–16% of the administered dose was excreted in the urine as unchanged drug. Plasma concentrations decline rapidly and the elimination half-life of nateglinide typically averaged 1.5 hours in all studies of Trazec in volunteers and type 2 diabetic patients. Consistent with its short elimination half-life, there is no apparent accumulation of nateglinide upon multiple dosing with up to 240 mg three times daily.

Food effect
When given post-prandially, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterised by a decrease in C_{max} and a delay in time to peak plasma concentration (t_{max}). It is recommended that Trazec be administered prior to meals. It is usually taken immediately (1 minute) before a meal but may be taken up to 30 minutes before meals.

Sub-populations
Elderly: Age did not influence the pharmacokinetic properties of nateglinide.

Hepatic impairment: The systemic availability and half-life of nateglinide in non-diabetic subjects with mild to moderate hepatic impairment did not differ to a clinically significant degree from those in healthy subjects.

Renal impairment: The systemic availability and half-life of nateglinide in diabetic patients with mild, moderate (creatinine clearance 31–50 ml/min) and severe (creatinine clearance 15–30 ml/min) renal impairment (not undergoing dialysis) did not differ to a clinically significant degree from those in healthy subjects. There is a 49% decrease in C_{max} of nateglinide in dialysis-dependent diabetic patients. The systemic availability and half-life in dialysis-dependent diabetic patients was comparable with healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

Gender: No clinically significant differences in nateglinide pharmacokinetics were observed between men and women.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to fertility and post-natal development. Nateglinide was not teratogenic in rats. In rabbits, at maternally toxic doses a higher incidence of foetuses with no gallbladder was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline
Povidone
Croscarmellose sodium
Magnesium stearate
Red iron oxide (E172)
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package.

6.5 Nature and contents of container

Blisters: PVC/PE/PVDC moulded foil with aluminium lidding foil.

Packs contain 12, 60, 84, 120 and 360 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/175/001
EU/1/01/175/004-007

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03.04.2001
Date of first renewal: 03.04.2006

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

TRAZEC 120 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 120 mg nateglinide.

Excipients:
Lactose monohydrate: 283 mg per tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

120 mg yellow, ovaloid tablets with "NVR" marked on one side and "TSL" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nateglinide is indicated for combination therapy with metformin in type 2 diabetic patients inadequately controlled despite a maximally tolerated dose of metformin alone.

4.2 Posology and method of administration

Nateglinide should be taken within 1 to 30 minutes before meals (usually breakfast, lunch and dinner).

The dosage of nateglinide should be determined by the physician according to the patient's requirements.

The recommended starting dose is 60 mg three times daily before meals, particularly in patients who are near goal HbA_{1c}. This may be increased to 120 mg three times daily.

Dose adjustments should be based on periodic glycosylated haemoglobin (HbA_{1c}) measurements. Since the primary therapeutic effect of Trazec is to reduce mealtime glucose, (a contributor to HbA_{1c}), the therapeutic response to Trazec may also be monitored with 1–2 hour post-meal glucose.

The recommended maximum daily dose is 180 mg three times daily to be taken before the three main meals.

Specific patient groups
Elderly
The clinical experience in patients over 75 years of age is limited.

Children and adolescents
There are no data available on the use of nateglinide in patients under 18 years of age, and therefore its use in this age group is not recommended.

Patients with hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. As patients with severe liver disease were not studied, nateglinide is contraindicated in this group.

Patients with renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment. Although there is a 49% decrease in C_{max} of nateglinide in dialysis patients, the systemic availability and half-life in diabetic subjects with moderate to severe renal insufficiency (creatinine clearance 15–50 ml/min) was comparable between renal subjects requiring haemodialysis and healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

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

4.3 Contraindications

Trazec is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients
- Type 1 diabetes (insulin-dependent diabetes mellitus, C-peptide negative)
- Diabetic ketoacidosis, with or without coma
- Pregnancy and breast-feeding (see section 4.6)
- Severe hepatic impairment

4.4 Special warnings and precautions for use

General
Nateglinide should not be used in monotherapy.

Like other insulin secretagogues, nateglinide is capable of producing hypoglycaemia.

Hypoglycaemia has been observed in patients with type 2 diabetes on diet and exercise, and in those treated with oral antidiabetic agents (see section 4.8). Elderly, malnourished patients and those with adrenal or pituitary insufficiency or severe renal impairment are more susceptible to the glucose-lowering effect of these treatments. The risk of hypoglycaemia in type 2 diabetic patients may be increased by strenuous physical exercise, or ingestion of alcohol.

Symptoms of hypoglycaemia (unconfirmed by blood glucose levels) were observed in patients whose baseline HbA_{1c} was close to the therapeutic target (HbA_{1C} <7.5%).

Combination with metformin is associated with an increased risk of hypoglycaemia compared to monotherapy.

Hypoglycaemia may be difficult to recognise in subjects receiving beta blockers.

When a patient stabilised on any oral hypoglycaemic agent is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, it may be necessary to discontinue oral hypoglycaemic treatment and replace it with insulin on a temporary basis.

Trazec contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, of the Lapp lactase deficiency or of glucose-galactose malabsorption should not take this medicine.

Specific patient groups
Nateglinide should be used with caution in patients with moderate hepatic impairment.

No clinical studies have been conducted in patients with severe hepatic impairment or children and adolescents. Treatment is therefore not recommended in these patient groups.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products influence glucose metabolism and possible interactions should therefore be taken into account by the physician:

The following agents may enhance the hypoglycaemic effect of nateglinide: angiotensin-converting enzyme inhibitors (ACEI).

The following agents may reduce the hypoglycaemic effect of nateglinide: diuretics, corticosteroids, and beta2 agonists.

When these medicinal products are administered to or withdrawn from patients receiving nateglinide, the patient should be observed closely for changes in glycaemic control.

Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

In an interaction trial with sulfinpyrazone, a CYP2C9 inhibitor, a modest increase in nateglinide AUC (~28%) was observed in healthy volunteers, with no changes in the mean C_{max} and elimination half-life. A more prolonged effect and possibly a risk of hypoglycaemia cannot be excluded in patients when nateglinide is co-administered with CYP2C9 inhibitors.

Particular caution is recommended when nateglinide is co-administered with other more potent inhibitors of CYP2C9, e.g. fluconazole or gemfibrozil, or in patients known to be poor metabolisers for CYP2C9.

Interaction studies with a 3A4 inhibitor have not been carried out *in vivo.*

In vivo, nateglinide has no clinically relevant effect on the pharmacokinetics of medicinal products metabolised by CYP2C9 and CYP3A4. The pharmacokinetics of warfarin (a substrate for CYP3A4 and CYP2C9), diclofenac (a substrate for CYP2C9), and digoxin were unaffected by coadministration with nateglinide. Conversely, these medicinal products had no effect on the pharmacokinetics of nateglinide. Thus, no dosage adjustment is required for digoxin, warfarin or other drugs that are CYP2C9 or CYP3A4 substrates upon coadministration with Trazec. Similarly, there was no clinically significant pharmacokinetic interaction of Trazec with other oral antidiabetic agents such as metformin or glibenclamide.

Nateglinide has shown a low potential for protein displacement in *in vitro* studies.

4.6 Pregnancy and lactation

Studies in animals have shown developmental toxicity (see section 5.3).

There is no experience in pregnant women, therefore the safety of Trazec in pregnant women cannot be assessed. Trazec, like other oral antidiabetic agents, is not recommended for use in pregnancy.

Nateglinide is excreted in the milk following a peroral dose to lactating rats. Although it is not known whether nateglinide is excreted in human milk, the potential for hypoglycaemia in breast-fed infants may exist and therefore nateglinide should not be used in lactating women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Based on the experience with nateglinide and with other hypoglycaemic agents, the following adverse reactions have been seen. Frequencies are defined as: common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000).

Hypoglycaemia
As with other antidiabetic agents, symptoms suggestive of hypoglycaemia have been observed after administration of nateglinide. These symptoms included sweating, trembling, dizziness, increased appetite, palpitations, nausea, fatigue, and weakness. These were generally mild in nature and easily handled by intake of carbohydrates when necessary. In completed clinical trials, symptoms of hypoglycaemia were reported in 10.4% with nateglinide monotherapy, 14.5% with nateglinide+metformin combination, 6.9% with metformin alone, 19.8% with glibenclamide alone, and 4.1% with placebo.

Immune system disorders
Rare: Hypersensitivity reactions such as rash, itching and urticaria.

Metabolism and nutrition disorders
Common: Symptoms suggestive of hypoglycaemia.

Gatrointestinal disorders
Common: Abdominal pain, diarrhoea, dyspepsia, nausea.
Uncommon: Vomiting.

Hepatobiliary disorders
Rare: Elevations in liver enzymes.

Other events
Other adverse events observed in clinical studies were of a similar incidence in Trazec-treated and placebo-treated patients.

Post-marketing data revealed very rare cases of erythema multiforme.

4.9 Overdose

In a clinical study in patients, Trazec was administered in increasing doses up to 720 mg a day for 7 days and was well tolerated. There is no experience of an overdose of Trazec in clinical trials. However, an overdose may result in an exaggerated glucose-lowering effect, with the development of hypoglycaemic symptoms. Hypoglycaemic symptoms without loss of consciousness or neurological findings should be treated with oral glucose and adjustments in dosage and/or meal patterns. Severe hypoglycaemic reactions with coma, seizure or other neurological symptoms should be treated with intravenous glucose. As nateglinide is highly protein-bound, dialysis is not an efficient means of removing it from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: D-phenylalanine derivative, ATC code: A10 BX 03

Nateglinide is an amino acid (phenylalanine) derivative, which is chemically and pharmacologically distinct from other antidiabetic agents. Nateglinide is a rapid, short-acting oral insulin secretagogue. Its effect is dependent on functioning beta cells in the pancreas islets.

Early insulin secretion is a mechanism for the maintenance of normal glycaemic control. Nateglinide,

when taken before a meal, restores early or first phase insulin secretion, which is lost in patients with type 2 diabetes, resulting in a reduction in post-meal glucose and HbA_{1c}.

Nateglinide closes ATP-dependent potassium channels in the beta-cell membrane with characteristics that distinguish it from other sulphonylurea receptor ligands. This depolarises the beta cell and leads to an opening of the calcium channels. The resulting calcium influx enhances insulin secretion. Electrophysiological studies demonstrate that nateglinide has 45–300-fold selectivity for pancreatic beta cell versus cardiovascular K^+_{ATP} channels.

In type 2 diabetic patients, the insulinotropic response to a meal occurs within the first 15 minutes following an oral dose of nateglinide. This results in a blood-glucose-lowering effect throughout the meal period. Insulin levels return to baseline within 3 to 4 hours, reducing post-meal hyperinsulinaemia.

Nateglinide-induced insulin secretion by pancreatic beta cells is glucose-sensitive, such that less insulin is secreted as glucose levels fall. Conversely, the coadministration of food or a glucose infusion results in an enhancement of insulin secretion.

In combination with metformin, which mainly affected fasting plasma glucose, the effect of nateglinide on HbA_{1c} was additive compared to either agent alone.

Nateglinide efficacy was inferior to that of metformin in monotherapy (decrease in HbA_{1c} (%) with metformin 500 mg three times daily monotherapy: –1.23 [95% CI: –1.48; –0.99] and with nateglinide 120 mg three times daily monotherapy –0.90 [95% CI: –1.14; –0.66]).

The efficacy of nateglinide in combination with metformin has been compared to the combination of gliclazide plus metformin in a 6-month randomised, double-blind trial in 262 patients using a superiority design. The decrease from baseline in HbA_{1c} was –0.41% in the nateglinide plus metformin group and –0.57% in the gliclazide plus metformin group (difference 0.17%, [95% CI –0.03, 0.36]). Both treatments were well tolerated.

An outcome study has not been conducted with nateglinide, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated.

5.2 Pharmacokinetic properties

Absorption and bioavailability

Nateglinide is rapidly absorbed following oral administration of Trazec tablets prior to a meal, with mean peak drug concentration generally occurring in less than 1 hour. Nateglinide is rapidly and almost completely (≥ 90%) absorbed from an oral solution. Absolute oral bioavailability is estimated to be 72%. In type 2 diabetic patients given Trazec over the dose range 60 to 240 mg before three meals per day for one week, nateglinide showed linear pharmacokinetics for both AUC and C_{max}, and t_{max} was independent of dose.

Distribution

The steady-state volume of distribution of nateglinide based on intravenous data is estimated to be approximately 10 litres. *In vitro* studies show that nateglinide is extensively bound (97–99%) to serum proteins, mainly serum albumin and to a lesser extent $alpha_1$-acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1–10 μg Trazec/ml.

Metabolism

Nateglinide is extensively metabolised. The main metabolites found in humans result from hydroxylation of the isopropyl side-chain, either on the methine carbon, or one of the methyl groups; activity of the main metabolites is about 5–6 and 3 times less potent than nateglinide, respectively. Minor metabolites identified were a diol, an isopropene and acyl glucuronide(s) of nateglinide; only the isopropene minor metabolite possesses activity, which is almost as potent as nateglinide. Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly

metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

Excretion
Nateglinide and its metabolites are rapidly and completely eliminated. Most of the [14C] nateglinide is excreted in the urine (83%), with an additional 10% eliminated in the faeces. Approximately 75% of the administered [^{14}C] nateglinide is recovered in the urine within six hours post-dose. Approximately 6–16% of the administered dose was excreted in the urine as unchanged drug. Plasma concentrations decline rapidly and the elimination half-life of nateglinide typically averaged 1.5 hours in all studies of Trazec in volunteers and type 2 diabetic patients. Consistent with its short elimination half-life, there is no apparent accumulation of nateglinide upon multiple dosing with up to 240 mg three times daily.

Food effect
When given post-prandially, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterised by a decrease in C_{max} and a delay in time to peak plasma concentration (t_{max}). It is recommended that Trazec be administered prior to meals. It is usually taken immediately (1 minute) before a meal but may be taken up to 30 minutes before meals.

Sub-populations
Elderly: Age did not influence the pharmacokinetic properties of nateglinide.

Hepatic impairment: The systemic availability and half-life of nateglinide in non-diabetic subjects with mild to moderate hepatic impairment did not differ to a clinically significant degree from those in healthy subjects.

Renal impairment: The systemic availability and half-life of nateglinide in diabetic patients with mild, moderate (creatinine clearance 31–50 ml/min) and severe (creatinine clearance 15–30 ml/min) renal impairment (not undergoing dialysis) did not differ to a clinically significant degree from those in healthy subjects. There is a 49% decrease in C_{max} of nateglinide in dialysis-dependent diabetic patients. The systemic availability and half-life in dialysis-dependent diabetic patients was comparable with healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

Gender: No clinically significant differences in nateglinide pharmacokinetics were observed between men and women.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to fertility and post-natal development. Nateglinide was not teratogenic in rats. In rabbits, at maternally toxic doses a higher incidence of foetuses with no gallbladder was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline
Povidone
Croscarmellose sodium
Magnesium stearate
Yellow iron oxide (E172)
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol

Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package.

6.5 Nature and contents of container

Blisters: PVC/PE/PVDC moulded foil with aluminium lidding foil.

Packs contain 12, 60, 84, 120 and 360 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/175/008
EU/1/01/175/011-014

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03.04.2001
Date of first renewal: 03.04.2006

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

TRAZEC 180 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 180 mg nateglinide.

Excipients:
Lactose monohydrate: 214 mg per tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

180 mg red, ovaloid tablets with "NVR" marked on one side and "TSX" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nateglinide is indicated for combination therapy with metformin in type 2 diabetic patients inadequately controlled despite a maximally tolerated dose of metformin alone.

4.2 Posology and method of administration

Nateglinide should be taken within 1 to 30 minutes before meals (usually breakfast, lunch and dinner).

The dosage of nateglinide should be determined by the physician according to the patient's requirements.

The recommended starting dose is 60 mg three times daily before meals, particularly in patients who are near goal HbA_{1c}. This may be increased to 120 mg three times daily.

Dose adjustments should be based on periodic glycosylated haemoglobin (HbA_{1c}) measurements. Since the primary therapeutic effect of Trazec is to reduce mealtime glucose, (a contributor to HbA_{1c}), the therapeutic response to Trazec may also be monitored with 1–2 hour post-meal glucose.

The recommended maximum daily dose is 180 mg three times daily to be taken before the three main meals.

Specific patient groups
Elderly
The clinical experience in patients over 75 years of age is limited.

Children and adolescents
There are no data available on the use of nateglinide in patients under 18 years of age, and therefore its use in this age group is not recommended.

Patients with hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. As patients with severe liver disease were not studied, nateglinide is contraindicated in this group.

Patients with renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment. Although there is a 49% decrease in C_{max} of nateglinide in dialysis patients, the systemic availability and half-life in diabetic subjects with moderate to severe renal insufficiency (creatinine clearance 15–50 ml/min) was comparable between renal subjects requiring haemodialysis and healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

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

4.3 Contraindications

Trazec is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients
- Type 1 diabetes (insulin-dependent diabetes mellitus, C-peptide negative)
- Diabetic ketoacidosis, with or without coma
- Pregnancy and breast-feeding (see section 4.6)
- Severe hepatic impairment

4.4 Special warnings and precautions for use

General
Nateglinide should not be used in monotherapy.

Like other insulin secretagogues, nateglinide is capable of producing hypoglycaemia.

Hypoglycaemia has been observed in patients with type 2 diabetes on diet and exercise, and in those treated with oral antidiabetic agents (see section 4.8). Elderly, malnourished patients and those with adrenal or pituitary insufficiency or severe renal impairment are more susceptible to the glucose-lowering effect of these treatments. The risk of hypoglycaemia in type 2 diabetic patients may be increased by strenuous physical exercise, or ingestion of alcohol.

Symptoms of hypoglycaemia (unconfirmed by blood glucose levels) were observed in patients whose baseline HbA_{1c} was close to the therapeutic target (HbA_{1C} <7.5%).

Combination with metformin is associated with an increased risk of hypoglycaemia compared to monotherapy.

Hypoglycaemia may be difficult to recognise in subjects receiving beta blockers.

When a patient stabilised on any oral hypoglycaemic agent is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, it may be necessary to discontinue oral hypoglycaemic treatment and replace it with insulin on a temporary basis.

Trazec contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, of the Lapp lactase deficiency or of glucose-galactose malabsorption should not take this medicine.

Specific patient groups
Nateglinide should be used with caution in patients with moderate hepatic impairment.

No clinical studies have been conducted in patients with severe hepatic impairment or children and adolescents. Treatment is therefore not recommended in these patient groups.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products influence glucose metabolism and possible interactions should therefore be taken into account by the physician:

The following agents may enhance the hypoglycaemic effect of nateglinide: angiotensin-converting enzyme inhibitors (ACEI).

The following agents may reduce the hypoglycaemic effect of nateglinide: diuretics, corticosteroids, and beta2 agonists.

When these medicinal products are administered to or withdrawn from patients receiving nateglinide, the patient should be observed closely for changes in glycaemic control.

Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

In an interaction trial with sulfinpyrazone, a CYP2C9 inhibitor, a modest increase in nateglinide AUC (~28%) was observed in healthy volunteers, with no changes in the mean C_{max} and elimination half-life. A more prolonged effect and possibly a risk of hypoglycaemia cannot be excluded in patients when nateglinide is co-administered with CYP2C9 inhibitors.

Particular caution is recommended when nateglinide is co-administered with other more potent inhibitors of CYP2C9, e.g. fluconazole or gemfibrozil, or in patients known to be poor metabolisers for CYP2C9.

Interaction studies with a 3A4 inhibitor have not been carried out *in vivo.*

In vivo, nateglinide has no clinically relevant effect on the pharmacokinetics of medicinal products metabolised by CYP2C9 and CYP3A4. The pharmacokinetics of warfarin (a substrate for CYP3A4 and CYP2C9), diclofenac (a substrate for CYP2C9), and digoxin were unaffected by coadministration with nateglinide. Conversely, these medicinal products had no effect on the pharmacokinetics of nateglinide. Thus, no dosage adjustment is required for digoxin, warfarin or other drugs that are CYP2C9 or CYP3A4 substrates upon coadministration with Trazec. Similarly, there was no clinically significant pharmacokinetic interaction of Trazec with other oral antidiabetic agents such as metformin or glibenclamide.

Nateglinide has shown a low potential for protein displacement in *in vitro* studies.

4.6 Pregnancy and lactation

Studies in animals have shown developmental toxicity (see section 5.3).

There is no experience in pregnant women, therefore the safety of Trazec in pregnant women cannot be assessed. Trazec, like other oral antidiabetic agents, is not recommended for use in pregnancy.

Nateglinide is excreted in the milk following a peroral dose to lactating rats. Although it is not known whether nateglinide is excreted in human milk, the potential for hypoglycaemia in breast-fed infants may exist and therefore nateglinide should not be used in lactating women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Based on the experience with nateglinide and with other hypoglycaemic agents, the following adverse reactions have been seen. Frequencies are defined as: common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000).

Hypoglycaemia
As with other antidiabetic agents, symptoms suggestive of hypoglycaemia have been observed after administration of nateglinide. These symptoms included sweating, trembling, dizziness, increased appetite, palpitations, nausea, fatigue, and weakness. These were generally mild in nature and easily handled by intake of carbohydrates when necessary. In completed clinical trials, symptoms of hypoglycaemia were reported in 10.4% with nateglinide monotherapy, 14.5% with nateglinide+metformin combination, 6.9% with metformin alone, 19.8% with glibenclamide alone, and 4.1% with placebo.

Immune system disorders
Rare: Hypersensitivity reactions such as rash, itching and urticaria.

Metabolism and nutrition disorders
Common: Symptoms suggestive of hypoglycaemia.

Gatrointestinal disorders
Common: Abdominal pain, diarrhoea, dyspepsia, nausea.
Uncommon: Vomiting.

Hepatobiliary disorders
Rare: Elevations in liver enzymes.

Other events
Other adverse events observed in clinical studies were of a similar incidence in Trazec-treated and placebo-treated patients.

Post-marketing data revealed very rare cases of erythema multiforme.

4.9 Overdose

In a clinical study in patients, Trazec was administered in increasing doses up to 720 mg a day for 7 days and was well tolerated. There is no experience of an overdose of Trazec in clinical trials. However, an overdose may result in an exaggerated glucose-lowering effect, with the development of hypoglycaemic symptoms. Hypoglycaemic symptoms without loss of consciousness or neurological findings should be treated with oral glucose and adjustments in dosage and/or meal patterns. Severe hypoglycaemic reactions with coma, seizure or other neurological symptoms should be treated with intravenous glucose. As nateglinide is highly protein-bound, dialysis is not an efficient means of removing it from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: D-phenylalanine derivative, ATC code: A10 BX 03

Nateglinide is an amino acid (phenylalanine) derivative, which is chemically and pharmacologically distinct from other antidiabetic agents. Nateglinide is a rapid, short-acting oral insulin secretagogue. Its effect is dependent on functioning beta cells in the pancreas islets.

Early insulin secretion is a mechanism for the maintenance of normal glycaemic control. Nateglinide,

when taken before a meal, restores early or first phase insulin secretion, which is lost in patients with type 2 diabetes, resulting in a reduction in post-meal glucose and HbA_{1c}.

Nateglinide closes ATP-dependent potassium channels in the beta-cell membrane with characteristics that distinguish it from other sulphonylurea receptor ligands. This depolarises the beta cell and leads to an opening of the calcium channels. The resulting calcium influx enhances insulin secretion. Electrophysiological studies demonstrate that nateglinide has 45–300-fold selectivity for pancreatic beta cell versus cardiovascular K^+_{ATP} channels.

In type 2 diabetic patients, the insulinotropic response to a meal occurs within the first 15 minutes following an oral dose of nateglinide. This results in a blood-glucose-lowering effect throughout the meal period. Insulin levels return to baseline within 3 to 4 hours, reducing post-meal hyperinsulinaemia.

Nateglinide-induced insulin secretion by pancreatic beta cells is glucose-sensitive, such that less insulin is secreted as glucose levels fall. Conversely, the coadministration of food or a glucose infusion results in an enhancement of insulin secretion.

In combination with metformin, which mainly affected fasting plasma glucose, the effect of nateglinide on HbA_{1c} was additive compared to either agent alone.

Nateglinide efficacy was inferior to that of metformin in monotherapy (decrease in HbA_{1c} (%) with metformin 500 mg three times daily monotherapy: –1.23 [95% CI: –1.48; –0.99] and with nateglinide 120 mg three times daily monotherapy –0.90 [95% CI: –1.14; –0.66]).

The efficacy of nateglinide in combination with metformin has been compared to the combination of gliclazide plus metformin in a 6-month randomised, double-blind trial in 262 patients using a superiority design. The decrease from baseline in HbA_{1c} was –0.41% in the nateglinide plus metformin group and –0.57% in the gliclazide plus metformin group (difference 0.17%, [95% CI –0.03, 0.36]). Both treatments were well tolerated.

An outcome study has not been conducted with nateglinide, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated.

5.2 Pharmacokinetic properties

Absorption and bioavailability

Nateglinide is rapidly absorbed following oral administration of Trazec tablets prior to a meal, with mean peak drug concentration generally occurring in less than 1 hour. Nateglinide is rapidly and almost completely (≥ 90%) absorbed from an oral solution. Absolute oral bioavailability is estimated to be 72%. In type 2 diabetic patients given Trazec over the dose range 60 to 240 mg before three meals per day for one week, nateglinide showed linear pharmacokinetics for both AUC and C_{max}, and t_{max} was independent of dose.

Distribution

The steady-state volume of distribution of nateglinide based on intravenous data is estimated to be approximately 10 litres. *In vitro* studies show that nateglinide is extensively bound (97–99%) to serum proteins, mainly serum albumin and to a lesser extent $alpha_1$-acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1–10 μg Trazec/ml.

Metabolism

Nateglinide is extensively metabolised. The main metabolites found in humans result from hydroxylation of the isopropyl side-chain, either on the methine carbon, or one of the methyl groups; activity of the main metabolites is about 5–6 and 3 times less potent than nateglinide, respectively. Minor metabolites identified were a diol, an isopropene and acyl glucuronide(s) of nateglinide; only the isopropene minor metabolite possesses activity, which is almost as potent as nateglinide. Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly

metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

Excretion
Nateglinide and its metabolites are rapidly and completely eliminated. Most of the [14C] nateglinide is excreted in the urine (83%), with an additional 10% eliminated in the faeces. Approximately 75% of the administered [^{14}C] nateglinide is recovered in the urine within six hours post-dose. Approximately 6–16% of the administered dose was excreted in the urine as unchanged drug. Plasma concentrations decline rapidly and the elimination half-life of nateglinide typically averaged 1.5 hours in all studies of Trazec in volunteers and type 2 diabetic patients. Consistent with its short elimination half-life, there is no apparent accumulation of nateglinide upon multiple dosing with up to 240 mg three times daily.

Food effect
When given post-prandially, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterised by a decrease in C_{max} and a delay in time to peak plasma concentration (t_{max}). It is recommended that Trazec be administered prior to meals. It is usually taken immediately (1 minute) before a meal but may be taken up to 30 minutes before meals.

Sub-populations
Elderly: Age did not influence the pharmacokinetic properties of nateglinide.

Hepatic impairment: The systemic availability and half-life of nateglinide in non-diabetic subjects with mild to moderate hepatic impairment did not differ to a clinically significant degree from those in healthy subjects.

Renal impairment: The systemic availability and half-life of nateglinide in diabetic patients with mild, moderate (creatinine clearance 31–50 ml/min) and severe (creatinine clearance 15–30 ml/min) renal impairment (not undergoing dialysis) did not differ to a clinically significant degree from those in healthy subjects. There is a 49% decrease in C_{max} of nateglinide in dialysis-dependent diabetic patients. The systemic availability and half-life in dialysis-dependent diabetic patients was comparable with healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

Gender: No clinically significant differences in nateglinide pharmacokinetics were observed between men and women.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to fertility and post-natal development. Nateglinide was not teratogenic in rats. In rabbits, at maternally toxic doses a higher incidence of foetuses with no gallbladder was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline
Povidone
Croscarmellose sodium
Magnesium stearate
Red iron oxide (E172)
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol

Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package.

6.5 Nature and contents of container

Blisters: PVC/PE/PVDC moulded foil with aluminium lidding foil.

Packs contain 12, 60, 84, 120 and 360 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/175/015
EU/1/01/175/018-021

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03.04.2001
Date of first renewal: 03.04.2006

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Farma S.p.A.
Via Provinciale Schito, 131
I-80058 Torre Annunziata - Napoli
Italy

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trazec 60 mg film-coated tablets
Nateglinide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 60 mg nateglinide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

12 film-coated tablets
60 film-coated tablets
84 film-coated tablets
120 film-coated tablets
360 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/175/001 12 film-coated tablets
EU/1/01/175/004 60 film-coated tablets
EU/1/01/175/005 84 film-coated tablets
EU/1/01/175/006 120 film-coated tablets
EU/1/01/175/007 360 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trazec 60 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Trazec 60 mg tablets
Nateglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trazec 120 mg film-coated tablets
Nateglinide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 120 mg nateglinide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

12 film-coated tablets
60 film-coated tablets
84 film-coated tablets
120 film-coated tablets
360 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/175/008 12 film-coated tablets
EU/1/01/175/011 60 film-coated tablets
EU/1/01/175/012 84 film-coated tablets
EU/1/01/175/013 120 film-coated tablets
EU/1/01/175/014 360 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trazec 120 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Trazec 120 mg tablets
Nateglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trazec 180 mg film-coated tablets
Nateglinide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 180 mg nateglinide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

12 film-coated tablets
60 film-coated tablets
84 film-coated tablets
120 film-coated tablets
360 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/175/015 12 film-coated tablets
EU/1/01/175/018 60 film-coated tablets
EU/1/01/175/019 84 film-coated tablets
EU/1/01/175/020 120 film-coated tablets
EU/1/01/175/021 360 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trazec 180 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Trazec 180 mg tablets
Nateglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Trazec 60 mgfilm-coated tablets
Trazec 120 mg film-coated tablets
Trazec 180 mg film-coated tablets
Nateglinide

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

In this leaflet:

1. WHAT TRAZEC IS AND WHAT IT IS USED FOR

Trazec is a medicine to lower blood sugar (glucose), which is taken by mouth (these medicines are also known as oral anti-diabetics).

It is used by people with type 2 diabetes. (This kind of diabetes is also called non-insulin-dependent diabetes mellitus.)

Insulin is a substance produced by a body organ called the pancreas. It helps to decrease blood sugar levels, especially after meals. In patients with type 2 diabetes, the body may not start producing insulin quickly enough after meals. Trazec works by stimulating the pancreas to produce insulin more quickly. This helps to keep the blood sugar controlled after meals.

Your doctor will prescribe Trazec together with another oral anti-diabetic containing metformin.

Trazec tablets start to act quickly after you take them and are eliminated from the body rapidly.

2. BEFORE YOU TAKE TRAZEC

Follow all instructions given to you by your doctor and pharmacist carefully, even if they are different from what is in this leaflet.

Do not take Trazec
- if you are allergic (hypersensitive) to nateglinide or any of the other ingredients of Trazec.
- if you have type 1 diabetes (i.e. your body does not produce any insulin).
- if you know that you have a severe liver problem.
- if you are pregnant or planning to become pregnant.
- if you are breast-feeding.

Talk to your doctor if you have any further questions or you think that any of these may apply to you.

Take special care with Trazec
People with diabetes sometimes get symptoms of low blood sugar (also called hypoglycaemia). Medicines, including Trazec, may also produce symptoms of low blood sugar.

If you get any of these symptoms – feeling dizzy, light-headed, hungry, shaky or any of the other signs in section 4, "Possible side effects" – eat or drink something containing sugar.

Some people are more likely to get symptoms of low blood sugar than others. Take care
- if you are over 65 years of age.
- if you are undernourished.
- if you have another medical condition that may cause low blood sugar (e.g. an under-active pituitary or adrenal gland).

If any of these apply to you, monitor your blood sugar levels more carefully.

Talk to your doctor
- if you know that you have a liver problem.
- if you have a severe kidney problem.
- if you have problems of drug metabolism.
- if you are due to have an operation.
- if you have suffered a fever, an accident or an infection.

Your treatment may need to be adjusted.

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

The amount of Trazec that you need may change if you take other medicines as these may cause your blood sugar levels to go up or down.

It is especially important that you tell your doctor or pharmacist if you are taking:
- Beta blockers or angiotensin-converting enzyme inhibitors (used, for example, to treat high blood pressure and certain heart conditions).
- Diuretics (used in the treatment of high blood pressure).
- Corticosteroids such as prednisone and cortisone (used to treat inflammatory disorders).
- Inhibitors of drug metabolism such as fluconazole (used to treat fungal infection), gemfibrozil (used to treat dyslipidaemia) or sulfinpyrazone (used to treat chronic gout).

Your doctor may adjust the dose of these medicines.

Food, drink and exercise
Take Trazec before meals (see section 3, "How to take Trazec"). Its effect may be delayed if it is taken during or after meals.

Even though you are taking medicines for your diabetes, it is important to keep following the diet and/or exercise your doctor has recommended for you.

Watch carefully for signs of low blood sugar, especially
- if you have exercised more strenuously than usual.
- if you have drunk alcohol.

Alcohol may upset the control of your blood sugar so you are advised to talk to your doctor about drinking alcohol while taking Trazec. If you do get symptoms of low blood sugar, eat or drink something containing sugar and talk to your doctor.

Trazec and older people
Trazec can be used by people over 65 years of age. Take special care to avoid low blood sugar.

Trazec and children and adolescents
Trazec is not recommended for children and adolescents (under 18 years of age) because its effects in this age group have not been studied.

Pregnancy and breast-feeding
Do not take Trazec if you are pregnant or planning to become pregnant. See your doctor as soon as possible if you become pregnant during treatment.

Do not breast-feed during treatment with Trazec.

Ask your doctor or pharmacist for advice before taking any medicine while you are pregnant or breast-feeding.

Driving and using machines
You are advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important if you have reduced or absent awareness of the warning signs of hypoglycaemia or if you have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

Important information about some of the ingredients of Trazec
Trazec tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE TRAZEC

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

When to take Trazec
Take Trazec before the three main meals, usually:
- 1 dose before breakfast
- 1 dose before lunch
- 1 dose before dinner

It is best to take it right before a main meal but you can take it up to 30 minutes before.

Do not take it if you are not going to eat a main meal. If you miss a meal, skip that dose of Trazec and wait until your next meal.

How much to take
Take Trazec as your doctor told you to. Your doctor will determine the dosage you require.

The usual dose of Trazec to start with is 60 mg before the three main meals. In some cases your doctor may prescribe higher doses. The recommended maximum daily dose is 180 mg three times daily to be taken before the three main meals.

Swallow the tablets whole with a glass of water before the meal.

How long to take Trazec
Take Trazec daily until your doctor tells you to stop.

If you take more Trazec than you should
If you have accidentally taken too many tablets, talk to a doctor straight away. If you experience symptoms of low blood sugar – if you feel dizzy, light-headed, hungry, shaky, or any of the other signs in section 4, “Possible side effects” – eat or drink something containing sugar.

If you feel as if you are about to have a severe hypoglycaemic attack (which may lead to loss of consciousness or seizure), call for urgent medical help – or make sure that someone else does this for you.

If you forget to take Trazec
If you forget to take a tablet simply take the next one before your next meal. Do not take a double dose of Trazec to make up for the one that you missed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Trazec can cause side effects, although not everybody gets them. The side effects caused by Trazec are usually mild to moderate.

The most common side effects are symptoms of low blood sugar (hypoglycaemia), which are usually mild. These include
- sweating,
- dizziness,
- shaking,
- weakness,
- hunger,
- feeling your heart beating fast,
- tiredness,
- feeling sick (nausea).

They can also be caused by lack of food or too high a dose of any anti-diabetic medicine you are taking. If you do get symptoms of low blood sugar, eat or drink something containing sugar.

Abdominal pain, indigestion, diarrhoea, nausea and vomiting have been reported.

Rare effects are mild abnormalities in liver function tests and allergic (hypersensitivity) reactions such as rash and itching.

A very rare effect is skin rash with blisters affecting the lips, eyes, mouth, sometimes with headache, fever and/or diarrhoea.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TRAZEC

Keep out of the reach and sight of children.
Store in the original package.
Do not use Trazec after the expiry date stated on the carton after EXP. The expiry date refers to the last day of that month.
Do not use any Trazec pack that is damaged or shows signs of tampering.
Do not store above 30°C.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Trazec contains
- The active substance is nateglinide.
- The other ingredients are lactose monohydrate; cellulose, microcrystalline; povidone; croscarmellose sodium; magnesium stearate and silica, colloidal anhydrous.
- The tablet coating contains hypromellose; titanium dioxide (E171); talc; macrogol and red (60 and 180 mg tablets) or yellow (120 mg tablets) iron oxide (E172).

What Trazec looks like and contents of the pack
Trazec 60 mg film-coated tablets are pink, round tablets with "NVR" marked on one side and "TS" on the other.

Trazec 120 mg film-coated tablets are yellow, ovaloid tablets with "NVR" marked on one side and "TSL" on the other.

Trazec 180 mg film-coated tablets are red, ovaloid tablets with "NVR" marked on one side and "TSX" on the other.

Each blister pack contains 12, 60, 84, 120 or 360 tablets. Not all pack sizes or tablet strengths may be available in your country.

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