NOVARTIS

Starlix®

Composition
Active substance: Nateglinide
Excipients: Tableting excipients

Pharmaceutical form and quantity of active substance per unit
Starlix: 60 mg film-coated tablets
Starlix: 120 mg film-coated tablets

Indications/Potential uses
Treatment of patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM) whose hyperglycaemia cannot be controlled by diet and/or physical exercise.
Starlix can be used as monotherapy, or in combination with metformin or a thiazolidinedione (glitazone, TZD).

Dosage and Administration
Nateglinide should be taken prior to each main meal. The main meal should be consumed within 30 minutes of ingestion of the tablet.
The response should be monitored by means of regular HbA_{1c} (glycosylated haemoglobin) measurements. Since the primary therapeutic effect of Starlix is to reduce post-meal blood glucose levels, the therapeutic effect may also be monitored on the basis of 1-2 hour post-meal blood glucose.

Monotherapy
The usual dose is 120 mg before each main meal.

Combination therapy
In patients prescribed nateglinide in combination with metformin or a thiazolidinedione, the recommended dose of nateglinide is 120 mg before meals. Dose reduction may be considered in patients who have attained an HbA_{1c} value of <7.5%.

Special dosage instructions
Dosage in elderly patients
No special dose adjustment is necessary in elderly patients (see **Pharmacokinetics**).

Children and adolescents
Safety and efficacy have not been investigated in children and adolescents.

Dosage in patients with hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment.
Patients with severe liver disease were not studied. Starlix should therefore not be used in this patient group (see **Pharmacokinetics**).

Dosage in patients with renal impairment
Dose adjustment is not necessary in patients with renal impairment (see **Pharmacokinetics**).

Contraindications
Starlix is contraindicated:
– In patients with hypersensitivity to the active substance or to any of the excipients.
– In patients with type 1 diabetes (insulin-dependent diabetes mellitus, IDDM) or diabetic ketoacidosis.
– During pregnancy and lactation (see **Pregnancy and Lactation**).

Warnings and Precautions
Hypoglycaemia may occur in patients treated with nateglinide (see **Adverse Effects**). Elderly, malnourished patients and patients with adrenal or pituitary insufficiency or severe renal impairment are more susceptible to glucose-lowering therapy. The risk of hypoglycaemia may be increased by strenuous physical exercise or ingestion of alcohol.
Combination with metformin or a thiazolidinedione may increase the risk of hypoglycaemia.
Hypoglycaemia may be difficult to recognize in patients receiving beta-blockers.

Interactions
Nateglinide inhibits the metabolism of tolbutamide, a CYP 2C9 substrate, *in vitro*.
No inhibition of CYP 3A4 is expected based on *in vitro* experiments.
Nateglinide has no clinically relevant effect on the pharmacokinetic properties of acenocoumarol and warfarin (substrates for CYP 2C9 and CYP 3A4), diclofenac (a substrate for CYP 2C9) or digoxin. Comedication of nateglinide with acenocoumarol was not found to affect the international normalized ratio (INR). Therefore, when Starlix is coadministered with digoxin, acenocoumarol or diclofenac, no dosage adjustment of these drugs or of Starlix is required.
Similarly, no clinically relevant pharmacokinetic interaction of Starlix with other oral antidiabetic agents, such as metformin or glibenclamide, was noted.
In an interaction study with sulfinpyrazone, a potent and selective CYP 2C9 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.
In an interaction study with concomitant administration of nateglinide and fluconazole, which inhibits both CYP 2C9 and CYP 3A4, there was a significant increase in nateglinide AUC (48%), with no changes in C_{max} and a reduction of 37% in the C_{max} of the active isopopene metabolite.
A prolonged effect and the potential risk of hypoglycaemia cannot be ruled out when nateglinide is given concomitantly with a CYP 2C9 inhibitor.
Nateglinide is highly bound to plasma proteins (98 %), mainly albumin. *In vitro* interaction studies with highly protein-bound drugs such as furosemide, propranolol, captopril, nicardipine, pravastatin, glibenclamide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide and metformin showed no influence on the extent of nateglinide protein binding. Similarly, nateglinide has no influence on the serum protein binding of propranolol, glibenclamide, nicardipine, warfarin, phenytoin, acetylsalicylic acid or tolbutamide.
A number of substances influence glucose metabolism. Possible interactions should therefore be taken into account by the physician:
The hypoglycaemic action of oral antidiabetic agents may be potentiated by NSAIDs, salicylates, MAO inhibitors and non-selective beta-adrenergic blocking agents.
The hypoglycaemic action of oral antidiabetic agents may be reduced by thiazides, corticosteroids, T_3 and T_4 products and sympathomimetics.
When these drugs are administered to or withdrawn from patients receiving nateglinide, the patient should be closely observed for changes in glycaemic control.

Pregnancy and Lactation
Reproduction studies in animals have shown no risk to the fetus but there have been no controlled studies in pregnant women. Like other oral antidiabetic agents, Starlix should not be used during pregnancy (see **Contraindications**).
Nateglinide is excreted in the milk following an oral dose to lactating animals. Although it is not known whether nateglinide is excreted in human milk, the potential for hypoglycaemia in breast-fed infants may exist. Starlix should therefore not be used in breast-feeding women.

Effects on ability to drive and use machines
Patients should be told about the risk of hypoglycaemia and advised to exercise particular caution when driving or using machines. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or who have frequent episodes of hypoglycaemia.

Adverse effects
Immune system
There have been isolated reports of hypersensitivity reactions such as rash, itching and urticaria.

Endocrine disorders
Symptoms of hypoglycaemia, such as sweating, trembling, confusion, increased appetite, palpitations, nausea, fatigue and a feeling of weakness, have been reported following ingestion of nateglinide. These symptoms were generally mild in nature and could be managed by intake of carbohydrates.
In clinical studies, symptomatic events – confirmed by blood glucose below 3.3 mmol/litre – were reported in 2.4% of patients.

Liver and gallbladder
There have been isolated reports of elevations in liver enzymes.

Other events
Most other frequently occurring adverse effects in clinical studies were of a similar incidence in the Starlix and placebo groups. They include gastrointestinal complaints (e.g. abdominal pain, dyspepsia, diarrhoea), headache, and conditions frequently occurring in this patient population, such as respiratory infections.

Overdose
In a clinical study, Starlix was administered in increasing doses up to 720 mg/day for 7 days and was well tolerated. There is no experience of an overdose of Starlix in clinical trials. An overdose would result in an increased glucose-lowering effect, with the development of hypoglycaemic symptoms. Hypoglycaemic symptoms without loss of consciousness or

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neurological findings should be treated with oral glucose and adjustments in dosage and/or meal patterns. Severe hypoglycaemic reactions with coma, epileptic seizure or other neurological symptoms must be treated with intravenous administration of 50% glucose solution. As nateglinide is highly protein-bound, dialysis is not an appropriate means of removing it from the blood.

Properties and Actions

ATC code: A10BX03

Mechanism of action / Pharmacodynamics

Nateglinide is an amino acid (phenylalanine) derivative which is chemically and pharmacologically distinct from other antidiabetic agents. It restores early insulin secretion, resulting in a reduction in post-meal glucose and HbA_{1c}. (glycosylated haemoglobin).

Early insulin secretion is an essential mechanism for the maintenance of normal glycaemic control. When taken before a meal, nateglinide restores early or first phase insulin secretion, which is lost in patients with type 2 diabetes. This action is mediated by a rapid and transient inactivation of the ATP-dependent potassium channels (K^+_{ATP} channels) on pancreatic beta-cells. Electrophysiological studies demonstrate that nateglinide has >300-fold selectivity for pancreatic beta-cell versus cardiovascular K^+_{ATP} channels.

Nateglinide induces significant insulin secretion within the first 15 minutes following a meal. This reduces post-meal glucose peaks. Insulin levels return to normal within 3 to 4 hours, thus reducing reactive 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 co-administration of food or a glucose infusion results in a clear enhancement of insulin secretion.

Clinical efficacy

In clinical studies Starlix monotherapy led to an improvement in glycaemic control. These results were determined on the basis of HbA_{1c} and post-meal glucose determinations. No experience with treatment lasting more than one year is available at present.

Compared with monotherapy with either substance, combination of Starlix with metformin, which mainly affects fasting blood glucose, resulted in an additive effect on the HbA_{1c} value, brought about by the complementary action of the two substances.

In a 24-week study, patients with type 2 diabetes who were insufficiently controlled on 8 mg/day rosiglitazone were additionally given either Starlix (120 mg three times daily before meals) or placebo. Compared to rosiglitazone monotherapy, combination therapy with Starlix and rosiglitazone resulted in more marked reduction in HbA_{1c} which was statistically significant. The difference was –0.76%.

Hypoglycaemia was observed in 4.5% of patients receivign rosiglitazone plus Starlix and 0% of patients receiving rosiglitazone plus placebo. No patient had to discontinue treatment. Mean weight gain compared to baseline was +3.1 kg in patients receiving the combination of Starlix and rosiglitazone and +1.1 kg in patients receiving placebo and rosiglitazone.

In a 24-week study, patients previously treated with high-dose sulphonylureas for at least 3 months were directly switched to monotherapy with Starlix. They experienced reduced glycaemic control, as evidenced by increases in fasting blood glucose and HbA_{1c}.

Combination of Starlix with sulphonylureas and switching from sulphonylureas to Starlix monotherapy cannot be recommended.

Pharmacokinetics

The pharmacokinetics of nateglinide are linear in the dose range of 60–240 mg three times daily.

Absorption

Nateglinide is rapidly absorbed following oral administration of the tablets prior to a meal. The peak plasma concentration is generally attained in less than one hour. Absolute bioavailability is about 72%.

Administration of nateglinide after meals does not affect total absorption (AUC). However, there is a delay in the rate of absorption characterized by a decrease in C_{max} and a delay in time to peak plasma concentration (t_{max}).

Distribution

The 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, α_{-1}-acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1–10 µg nateglinide/ml.

Metabolism

Nateglinide is extensively metabolised. Oxidative metabolism is primarily by CYP 2C9 (70%), with involvement of CYP 3A4 to a lesser extent (30%).

The main metabolites result from hydroxylation of the isopropyl side-chain, either on the methine carbon or on one of the methyl groups. Activity of the main metabolites is about 5-6 and 3 times less potent, respectively, than that of nateglinide. Minor metabolites identified were a diol, an isopropene (dehydro derivative) and an acyl glucuronide. Only the isopropene minor metabolite possesses activity similar to that of nateglinide.

Elimination

Nateglinide and its metabolites are rapidly and completely eliminated. Approximately 75% of the administered [^{14}C] nateglinide is excreted in the urine within six hours post-dose. Most of the [14C] nateglinide is excreted in the urine (83%), with an additional 10% eliminated in the faeces.

Approximately 6-16% of the administered dose is excreted in the urine as unchanged drug. Plasma concentrations decline rapidly and the elimination half-life of nateglinide averages 1.5 hours in all studies in volunteers and type 2 diabetic patients. Owing to this short half-life, there is no accumulation of nateglinide upon multiple dosing with up to 240 mg three times daily.

Pharmacokinetics in special clinical situations

Elderly patients: Age does not influence pharmacokinetic parameters. No difference in the safety and efficacy profile has been observed between elderly patients and the general population.

Children and adolescents: The pharmacokinetics of Starlix have not been investigated in children and adolescents.

Patients with hepatic impairment: The systemic availability and the half-life of nateglinide in persons with mild to moderate hepatic impairment do not differ to a clinically significant degree from those in healthy subjects. Patients with severe liver disease were not studied.

Patients with renal impairment: The systemic availability and the half-life of nateglinide in diabetic subjects with moderate to severe renal impairment (creatinine clearance 15–50 ml/min/1.73 m^2) and in patients requiring dialysis do not differ to a clinically significant degree from those in healthy subjects.

Preclinical 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 reproduction.

Other information

Shelf-life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

See folding box.

Pack sizes

Country specific pack sizes

Manufacturer

See folding box

Information last revised

March 2004

Approval date (text)

12 July 2004

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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