Product Monograph

PrStarlix*

(nateglinide)

60, 120 and 180 mg Tablets

THERAPEUTIC CLASSIFICATION

Oral Antidiabetic Agent

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ACTIONS AND CLINICAL PHARMACOLOGY

Starlix (nateglinide) is an amino acid derivative that improves glycemic control by restoring early insulin secretion. Nateglinide induces significant insulin secretion within the first 15 minutes following a meal. Early insulin secretion results in suppression of hepatic glucose production, reducing meal-related glucose excursions and post-meal hyperinsulinemia which has been associated with delayed hypoglycemia.

Early insulin secretion is an essential mechanism to maintain normal glycemic control. The loss of early insulin secretion characterizes Type 2 diabetes. Nateglinide when taken just before meals restores early insulin secretion through a rapid and transient interaction with the ATP-sensitive potassium (K^+_{ATP}) channel on pancreatic ß-cells. Electrophysiologic studies demonstrate that nateglinide has > 300-fold selectivity for pancreatic ß-cell versus cardiovascular K^+_{ATP} channels. The extent of insulin release is dependent on ambient glucose concentrations such that less insulin is secreted as glucose levels fall. The action of nateglinide is dependent upon functioning beta cells in the pancreatic islets.

Pharmacokinetics

Absorption

Following oral administration prior to a meal, nateglinide is rapidly absorbed with mean peak plasma drug concentrations (C_{max}) generally occurring within 1 hour to peak plasma concentration (T_{max}) after dosing . When administered to patients with Type 2 diabetes over the dosage range of 60 to 240 mg three times a day for one week, nateglinide demonstrated linear pharmacokinetics for both AUC (area under the time/plasma concentration curve) and C_{max}. T_{max} was found to be independent of dose in this patient population. Absolute bioavailability is estimated to be 73%. When given with meals, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in C_{max} and a delay in time to T_{max}. Nateglinide is usually taken immediately (1 minute) before a meal but may be taken up to 30 minutes before meals (See Dosage and Administration).

Distribution

Based on intravenous (IV) data, the steady state volume of distribution of nateglinide is estimated to be approximately 10 liters. Nateglinide is extensively bound (98%) to serum proteins, primarily serum albumin and to a lesser extent $\propto_1$ acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1-10 μg/mL.

Metabolism

Nateglinide is extensively metabolized by the mixed-function oxidase system prior to elimination. The major routes of metabolism are hydroxylation followed by glucuronide conjugation. The major metabolites are less potent than nateglinide. The isoprene minor metabolite possesses similar potency as the parent compound nateglinide.

Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly metabolized by cytochrome P_{450} isoenzyme CYP2C9 (70%) and to a lesser extent by CYP 3A4 (30%) (See Precautions - Drug Interactions).

Excretion

Nateglinide and its metabolites are rapidly and completely eliminated following oral administration. Within 6 hours after dosing, approximately 75% of the administered ^{14}C-nateglinide is recovered in the urine. Most of the ^{14}C-nateglinide (83%) is excreted in the urine with an additional 10% eliminated in the feces. Approximately 16% of the ^{14}C-nateglinide is excreted in the urine as parent compound. In all studies of healthy volunteers and patients with Type 2 diabetes, nateglinide plasma concentrations declined rapidly with an average elimination half-life of 1.5 hours. Consistent with this short elimination half-life, there is no apparent accumulation of nateglinide upon multiple dosing of up to 240 mg three times daily for 7 days.

Special Populations

Geriatric: There was no difference in the safety and efficacy profile of nateglinide between the elderly and the general population. In addition, age did not influence the pharmacokinetic properties of nateglinide. Therefore, no special dose adjustments are necessary for elderly patients.

Gender: No clinically significant differences in nateglinide pharmacokinetics were observed between men and women. Therefore, no dose adjustment based on gender is needed.

Race: Results of a population pharmacokinetic analysis included subjects of Caucasian (n=255), black (n=12) and other ethnic origins (n=45). The results did not indicate any influence of race on the pharmacokinetics of nateglinide, but the numbers are small.

Renal Impairment: The systemic availability and the half-life of nateglinide in diabetic subjects with moderate to severe renal insufficiency (CrCl: 0.25-0.83 mL/sec/1.73 m^2 or 15-50 mL/min/1.73m^2), whether or not on dialysis, do not differ to a clinically significant extent, from those in healthy subjects, therefore no dose adjustment is necessary.

Hepatic Impairment: The systemic availability and the half-life of nateglinide in non-diabetic subjects with mild to moderate hepatic insufficiency do not differ to a clinically significant extent from those in healthy subjects. Consequently, dose adjustment for patients with mild to moderate hepatic disease is not required. Since patients with moderate to severe hepatic disease were not studied, nateglinide should be used with caution in such patients.

Pharmacodynamics and Clinical Effects

In clinical studies, treatment with nateglinide resulted in an improvement in glycemic control, as measured by glycosylated hemoglobin A1c (HbA_{1c}) and post-meal glucose. Fasting plasma glucose (FPG) levels were also reduced. This is consistent with the mechanism of action of nateglinide which is to restore early insulin secretion and thereby reduce post-meal glucose. The improvement in glycemic control was durable, with maintenance of effect compared to baseline for at least 52 weeks. In the 24-week, placebo-controlled, clinical trials, the mean weight gain in patients treated with nateglinide was 1 kg or less.

Clinical Studies

Compared to repaglinide in healthy subjects nateglinide was associated with a faster rise of insulin concentrations, (within 30 minutes), and a shorter duration, (return to placebo levels in 1.5 versus 4 hours), resulting in less total insulin exposure. Nateglinide was also more effective in blunting the post-meal plasma glucose excursion compared to repaglinide (89% vs 56%) without inducing prolonged hypoglycemia.

The loss of first phase insulin secretion is a hallmark of Type 2 diabetes. Nateglinide restores this response in patients with Type 2 diabetes.

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated in patients with Type 2 diabetes that improved glycemic control, as reflected in HbA_{1C} and fasting glucose levels, was associated with a reduction in the diabetic complications retinopathy, neuropathy and nephropathy.

The DECODE study (Diabetes Epidemiology Collaborative Analysis of diagnostic Criteria in Europe study published in 1999) and the Diabetes Intervention Study demonstrated the role of 2-hour plasma glucose as an independent risk factor for total and cardiovascular mortality whereas FPG did not significantly contribute to the prediction of mortality.

A total of 2122 patients with Type 2 diabetes were treated with **Starlix** in double-blind, placebo or active-controlled studies. These studies included two 24-week placebo controlled studies, two 24-week active controlled studies, and five additional efficacy studies with treatment durations of 8 weeks (2 studies), 12 weeks (2 studies) or 16 weeks. In addition, three controlled extension studies were carried out to 52 weeks. All nine studies were characterized by a lengthy washout period of prior therapy so as to adequately evaluate the treatment effect of **Starlix** by minimizing confounding effects of previous antidiabetic medications. In these studies, **Starlix** was administered before main meals, usually breakfast, lunch and dinner.

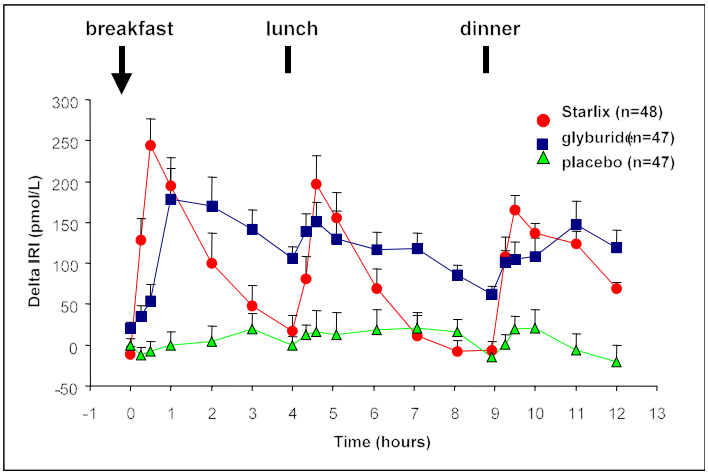
Effect on post-meal (prandial) plasma glucose

Restoration of early insulin release during meals, resulting in reduced post-meal plasma glucose, is an important component of optimal therapy in Type 2 diabetes.

In an 8-week study that compared the effect of **Starlix** 120 mg taken with meals, glyburide 10 mg once daily, and placebo on daytime glucose and insulin profiles, treatment with

Starlix was associated with a greater reduction of the post-meal glucose excursion and less total insulin exposure.

Unadjusted Insulin Levels-Change from Baseline (Pretreatment)



The rapid rise and short duration of insulin release associated with **Starlix** results in a reduction in glucose fluctuations throughout the day. **Starlix** significantly reduced the standard deviation of the plasma glucose levels compared to glyburide. The results illustrated in the figure above suggest that the postprandial insulin pattern in response to **Starlix** approximates the physiological pattern.

After a liquid (Sustacal®, Mead Johnson) meal, both **Starlix** and glyburide reduced the incremental glucose exposure over four hours. This reduction was statistically significantly greater for **Starlix** compared to glyburide (i.e. The percent change from baseline AUC_{0-4} was -64%, -32% and -1% for **Starlix**, glyburide and placebo respectively).

In a 24-week, placebo-controlled study conducted to evaluate the effect of **Starlix** as monotherapy and in combination with metformin, there was a statistically significant reduction in incremental mealtime plasma glucose $AUC_{(0\text{-}130\ min)}$. The post-meal glycemic

excursion was reduced by 16 % with metformin, 34% with **Starlix** 120 mg before meals and by 40% with the combination of **Starlix** 120 mg before meals plus metformin 500 mg tid. These data confirm that the efficacy of **Starlix** in lowering post-meal glucose is maintained when administered with a drug with a complementary mode of action.

Monotherapy

Two 24-week, placebo-controlled studies were conducted in patients with Type 2 diabetes that were inadequately controlled on diet alone. In Study A, statistically significant reductions in HbA_{1c} occurred in a dose-dependent manner over the range of 60 to 180 mg when **Starlix** was administered just before breakfast, lunch, and dinner as monotherapy. The mean change from baseline for reduction of HbA_{1c} was 0.004 to 0.006 (0.4 to 0.6%). The difference from placebo was 0.006 to 0.01 (0.6 to 1.0%) for 120 mg **Starlix** before breakfast, lunch, and dinner. Statistically significant reductions in fasting plasma glucose (FPG) over the range of 0.61 to 0.93 mmol/L were also observed.

In a second 24-week study (Study B) conducted to evaluate the effect of **Starlix** monotherapy, the mean change from baseline for reduction of HbA_{1c} was 0.005 (0.5 %). The difference from placebo was 0.009 (0.9%) for 120 mg **Starlix** before breakfast, lunch, and dinner, which was statistically significant.

Combination with Metformin

The results of the above study (Study B) suggest that **Starlix** and metformin are synergistic when used in combination, due to complementary modes of action. The combination of the two drugs demonstrated an 84% responder rate based on a reduction of >10% from pretreatment baseline HbA_{1C}. The effect on HbA_{1c} and FPG was greater with **Starlix** plus metformin combination therapy than with either agent alone. Virtually all of the post-meal glucose effect was due to **Starlix**. Metformin had a greater effect on HbA1c than nateglinide.

Other

In a 24-week active controlled study, patients who were stabilized on high dose sulfonylurea for at least three months and directly switched to monotherapy with **Starlix** 60 or 120 mg before meals experienced reduced glycemic control as evidenced by increases in FPG and HbA_{1c}.

In a 12-week study of patients inadequately controlled on glyburide 10 mg once daily, the addition of **Starlix** 120 mg before meals did not produce any additional benefit.

INDICATIONS AND CLINICAL USE

Starlix (nateglinide) is indicated as monotherapy in addition to diet and exercise to lower the blood sugar in patients with type 2 diabetes mellitus who are not controlled satisfactorily by diet and exercise alone.

Starlix (nateglinide) is indicated also in combination with metformin in patients not controlled satisfactorily on diet, exercise, and either nateglinide or metformin alone.

Management of Type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of Type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with **Starlix**, secondary causes of poor glycemic control, e.g., infection, should be investigated and treated.

CONTRAINDICATIONS

Starlix (nateglinide) is contraindicated in patients with:

1. Known hypersensitivity to the drug or its inactive ingredients.
2. Type 1 diabetes.
3. Diabetic ketoacidosis.

PRECAUTIONS

Hypoglycemia: Hypoglycemia has been observed in patients with Type 2 diabetes treated with oral antidiabetic agents. Geriatric patients, 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 hypoglycemia may be increased by strenuous physical exercise, ingestion of alcohol, and/or insufficient caloric intake.

Combination with other oral antidiabetic agents may increase the risk of hypoglycemia.

Hypoglycemia may be difficult to recognize in elderly subjects and in subjects receiving β-blockers.

Starlix should be used with caution in patients with moderate to severe hepatic impairment because such patients have not been studied.

Use in Pregnancy

Nateglinide was not teratogenic in rats at doses up to 1000 mg/kg (20 times the maximum daily human dose when compared on the basis of body surface area). In the rabbit, embryonic development was adversely affected and the incidence of gallbladder agenesis or small gallbladder was increased at a dose which also resulted in maternal toxicity (i.e., 500 mg/kg, which is 21 times the maximum daily human dose based on body surface area.

There are no adequate and well-controlled studies in pregnant women. **Starlix** is not recommended for use in pregnancy.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

Studies in lactating rats showed that nateglinide is excreted in the milk; the AUC_{0-48h} ratio in milk to plasma was about 1.4. Body weights were lower in offspring of rats administered nateglinide at 1000 mg/kg during the peri- and postnatal period. It is not known whether **Starlix** is excreted in human milk. Because many drugs are excreted in human milk, **Starlix** should not be administered to a nursing woman.

Use in Children

The safety and effectiveness of **Starlix** in pediatric patients have not been established.

Use in the Elderly

Among patients receiving **Starlix** as monotherapy in controlled clinical studies ranging from 8 weeks to 1 year in duration, 436 patients (30%) were 65 or older and 80 patients (5.4%) were 75 or older. No differences in safety or efficacy between these subjects and those less than 65 were observed for **Starlix**. There was no increase in frequency of hypoglycemia in patients over the age of 65. However, greater sensitivity of some older individuals to **Starlix** therapy cannot be ruled out.

Drug Interactions

Data available from both *in vitro* and *in vivo* drug metabolism experiments indicate that nateglinide is predominantly metabolized by the cytochrome p450 isoenzyme CYP2C9 (70%) and to a lesser extent by CYP3A4 (30%). Nateglinide has the ability to inhibit the *in vitro* metabolism of tolbutamide, a CYP2C9 substrate. No inhibition of CYP 3A4 metabolic reactions is expected based on *in vitro* experiments, suggesting a low potential for clinically significant pharmacokinetic drug interactions.

Glyburide: Concomitant administration of **Starlix** (120 mg t.i.d) and glyburide (10 mg/day) to healthy volunteers had no clinically relevant effect on the pharmacokinetics of either agent.

Metformin: In healthy volunteers, **Starlix** (120 mg t.i.d) taken with metformin (500 mg/day) did not alter the pharmacokinetics of either agent.

Digoxin: **Starlix** (120 mg t.i.d) when administered with digoxin (1 mg/day) to healthy volunteers, did not alter the steady-state pharmacokinetic properties of either agent.

Warfarin: **Starlix** (120 mg t.i.d) taken with warfarin (30 mg/day) by healthy volunteers had no clinically relevant effect on the pharmacokinetics of either agent.

Diclofenac: Administration of **Starlix** (120 mg b.i.d) with diclofenac (75 mg/day) to healthy volunteers did not alter the pharmacokinetics of either agent.

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

Starlix is highly bound to plasma proteins (98 %), mainly albumin. In an *in vitro* displacement study with highly protein-bound drugs such as furosemide, propranolol, captopril, nicardipine, pravastatin, glyburide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide, and metformin, there was no influence by these drugs on the extent of nateglinide protein binding. In a separate *in vitro* study, **Starlix** had no influence on the serum protein binding of propranolol, glyburide, nicardipine, warfarin, phenytoin, acetylsalicylic acid, and tolbutamide.

Certain drugs, including nonsteroidal anti-inflammatory agents, salicylates, monoamine oxidase inhibitors, and non-selective beta-adrenergic-blocking agents may potentiate the hypoglycemic action of oral antidiabetic drugs.

Certain drugs including thiazides, corticosteroids, thyroid products and sympathomimetics may reduce the hypoglycemic action of oral antidiabetic drugs.

When these drugs are administered to or withdrawn from patients receiving **Starlix**, the patient should be observed closely for changes in glycemic control.

Food Interactions

The pharmacokinetics of **Starlix** are not affected by the composition of a meal (high protein, fat or carbohydrate). **Starlix** does not have any effect on gastric emptying.

Information for Patients

Patients should be informed of the following:

Management of Type 2 diabetes should include adherence to dietary instructions, regular exercise and routine testing of blood glucose and glycosylated hemoglobin (HbA_{1c}).

All oral antidiabetic treatments have the potential to cause hypoglycemia. Geriatric patients, malnourished patients and those with adrenal or pituitary insufficiency are more susceptible to the glucose lowering effects of these treatments. A missed or delayed meal, strenuous physical exercise, or concomitant use of oral antidiabetic agents may increase the risk of hypoglycemia. Patients experiencing hypoglycemia should not drive or operate machinery. Hypoglycemia may be difficult to recognize in elderly patients and in patients receiving ß-blockers.

Starlix should be taken before meals and is usually taken immediately (1 minute) before meals but may be taken up to 30 minutes before meals. Patients who skip a meal should be instructed to skip a dose for that meal.

Laboratory Tests

Since the primary mechanism of action for **Starlix** is reducing post-meal glucose (an essential contributor to HbA_{1c}), the therapeutic response to **Starlix** may be monitored with 1-2 hour post-meal glucose measurements. In addition, glycosylated hemoglobin (HbA_{1c}) should also be measured periodically.

ADVERSE REACTIONS

Starlix (nateglinide) was administered either as monotherapy or combination therapy to 2122 patients with Type 2 diabetes including 1791 exposed for at least 12 weeks, 1224 for at least 24 weeks and 190 for 52 weeks. Of these, 1136, 789 and 113 patients were exposed to **Starlix** monotherapy for 12, 24 and 52 weeks respectively.

Discontinuation due to adverse events occurred in 4.9% of **Starlix** treated patients vs 5.5% in patients receiving placebo. Among **Starlix** treated patients, the most common reasons for discontinuation were fatigue (0.8%), thirst (0.7%), and polyuria (0.5). Only 0.3% of **Starlix** treated patients discontinued due to hypoglycemia.

The following table list common adverse events for **Starlix** patients, regardless of attribution, in placebo controlled studies and active controlled studies (i.e metformin and glyburide) of up to 24 weeks in duration.

Commonly reported adverse events (% of Patients)*

EVENT	Placebo controlled studies		Active controlled studies		
	Starlix N=973	Placebo N=458	**Starlix** N=378	Metformin N=194	Glyburide N=243
Body as A Whole-General Disorders					
Accidental trauma	2.7	1.7	1.9	1.0	5.3

Central and Peripheral Nervous System Disorders					
Dizziness	3.6	2.2	3.7	1.5	3.7
Gastrointestinal					
Abdominal Pain	3.1	3.1	2.1	0.5	0.8
Dyspepsia	2.5	2.2	0.5	2.1	1.2
Metabolic					
Hypoglycemia (confirmed)**	2.8	0.4	0.3	0.5	5.3
Musculoskeletal					
Arthropathy	2.7	2.2	1.3	3.1	2.5
Respiratory					
Coughing	2.2	2.2	0.5	2.6	2.5
Upper resp tract infection	10.4	8.1	6.9	3.6	10.3

*Events ≥2% for the **Starlix** group in the placebo-controlled studies and = events in the placebo group

** Any symptomatic event confirmed by a plasma glucose equivalent of ≤ 3.3 mmol/L

The most frequently occurring symptoms of hypoglycemia among patients who received **Starlix** were tremor, increased sweating, dizziness, and asthenia. These events were generally mild; most events took place during the day, within 4 hours of the previous meal and drug intake.

Rare cases of elevations in liver enzymes were reported.

Rare cases of hypersensitivity reactions such as rash, itching and urticaria were reported.

In all completed clinical studies there was no relation of dose on the overall incidence of adverse experiences.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In a clinical study in patients with Type 2 diabetes, **Starlix** (nateglinide) was administered in increasing doses up to 720 mg a day for 7 days and there was no clinically significant adverse events reported. There have been no instances of overdose with **Starlix** in clinical trials. However, an overdose may result in an exaggerated glucose lowering effect with the development of hypoglycemic symptoms. Hypoglycemic symptoms without loss of consciousness or neurological findings should be treated with oral glucose and adjustments in dosage and/or meal patterns. Severe hypoglycemic 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.

DOSAGE AND ADMINISTRATION

Starlix (nateglinide) should be taken prior to meals. It is usually taken immediately (1 minute) before a meal but may be taken up to 30 minutes before meals.

Monotherapy
The usual starting and maintenance dose is 120 mg before meals.

If an adequate response is not achieved, a dose of 180 mg before meals may be used or metformin may be added to the current dose (see **Combination Therapy with Metformin**). The 60 mg dose of **Starlix** may be used in patients who are neal goal HbA_{1c} (e.g. $HbA_{1c} < 0.075$), when treatment is initiated.

Since the primary mechanism of **Starlix** is reducing mealtime glucose (an essential contributor to HbA_{1c}), the therapeutic response to **Starlix** may be monitored with 1-2 hour post-meal glucose. In addition, glycosylated hemoglobin (HbA_{1c}) should be measured periodically.

Combination Therapy with Metformin

For patients on **Starlix** monotherapy who require additional therapy, metformin may be added to the maintenance dose.

For patients on metformin monotherapy who require additional therapy, the usual dose of **Starlix** is 120 mg before meals. For some patients who are close to their therapeutic target (e.g. $HbA_{1C} < 0.075$), **Starlix** 60 mg before meals may be sufficient.

Dosage in the elderly

No special dose adjustments are usually necessary.

Dosage in renal and hepatic impairment

No dosage adjustment is necessary in patients with mild to severe renal insufficiency or in patients with mild hepatic insufficiency. Dosing of patients with moderate to severe hepatic dysfunction has not been studied. Therefore, Starlix should be used with caution in patients with moderate to severe liver disease.

INFORMATION FOR THE CONSUMER

What is **Starlix** and what does **Starlix** do?

Starlix tablet contains the active substance nateglinide. **Starlix** tablets also contain the following non-medicinal ingredients : colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide (red or yellow), lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc and titanium dioxide.

Starlix is a medicine to lower blood sugar (glucose), which is taken by mouth (such medicines are known as oral antidiabetics).

It is used in patients with type 2 diabetes whose condition cannot be controlled by diet and exercise alone. This kind of diabetes is also called non-insulin-dependent diabetes mellitus.

Insulin (produced by an organ called the pancreas) is a substance, which helps to decrease blood sugar levels, especially after meals. In patients with type 2 diabetes, the body does not respond well to insulin and may not start to make it quickly enough after meals. **Starlix** works by stimulating the pancreas to produce insulin more quickly and this helps to keep the blood sugar controlled after meals.

Your doctor will prescribe **Starlix** either by itself or together with metformin if one medicine alone is not sufficient to control your blood sugar levels. Even though you are now starting a medicine for your diabetes, it is important that you continue to follow the diet and/or exercise advised for you.

Starlix tablets start to act within a very short time after intake and are eliminated from the body rapidly.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.

Before you take Starlix

Follow all instructions given to you by your doctor or pharmacist carefully.

Read the following information before you take **Starlix**.

Do not take Starlix

- If you are allergic (hypersensitive) to nateglinide or any of the other ingredients of **Starlix**
- If you have type 1 diabetes (i.e. your body does not produce any insulin)
- If you have diabetic ketoacidosis.
- 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 Starlix

Tell your doctor before you take Starlix

- If you have a liver problem
- If you have kidney problems

Diabetic patients may develop symptoms associated with low blood sugar (also known as hypoglycemia). These symptoms include sweating, dizziness, shaking, weakness, hunger, palpitations (perceivable and fast heart beat), tiredness and nausea.

Oral antidiabetic drugs, including **Starlix**, may also produce symptoms of hypoglycemia. Certain patients are more sensitive to this effect of antidiabetic treatment than others. These include patients who have exercised more strenuously than usual or drunk alcohol, who are elderly or undernourished, who are taking other oral antidiabetics, or who have another medical condition that may cause low blood sugar (e.g. an underactive pituitary or adrenal gland or kidney problems).

- If any of these conditions apply to you, talk to your doctor about it. Your blood sugar level might need to be more carefully monitored.

Taking Starlix with food and drink

Take **Starlix** before meals (see under section "When to take **Starlix**"); its effect may be delayed if it is taken during or after meals.

Since alcohol may disturb the control of your blood sugar, you are advised to talk to your doctor about this.

Use in the elderly

Starlix can be used by elderly patients.

Use in children

The use of **Starlix** in children has not been studied and therefore it is not recommended.

Pregnancy

Consult your doctor as soon as possible if you become pregnant during treatment.

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

Breast-feeding

Do not breast-feed during treatment with **Starlix**.

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

Driving and using machines

All diabetic patients who drive need to be particularly careful to avoid low blood sugar. If you experience symptoms of low blood sugar you should not drive or use machines.

Taking other medicines

Tell your doctor or pharmacist about any other medicines you are taking or have recently taken, including any you have bought without a prescription.

Other medicines may affect the actions of **Starlix** and, conversely, **Starlix** may affect the actions of other medicines. This may result in an increase or a decrease in your blood sugar levels.

It is particularly important that you tell your doctor or pharmacist if you are taking any of the following:

- Nonsteroidal anti-inflammatory agents (used, for example, to treat muscle and joint pain).
- Salicylates such as aspirin (used as pain-killers).
- Monoamine oxidase inhibitors (used to treat depression).
- Beta-blockers (used, for example, to treat high blood pressure and certain heart conditions).
- Thiazides (used in the treatment of high blood pressure).
- Corticosteroids such as prednisone and cortisone (used to treat inflammatory disorders).
- Thyroid products (used to treat patients with low production of thyroid hormones).

- Sympathomimetics (used, for example, to treat asthma).
- Sulfinpyrazone (used to treat chronic gout).

Your doctor may adjust the dose of these medicines.

How to use Starlix

Follow all instructions given to you by your doctor and pharmacist carefully. Do not take more **Starlix** than your doctor has prescribed.

How much to take

The usual dose of **Starlix** is 120 mg before main meals (usually breakfast, lunch and dinner). A lower dose of 60 mg may be considered if your blood sugar levels are near the normal values. The maximum recommended dose is 180 mg before main meals. Your doctor may need to adjust the dosage to your particular needs.

He/she will prescribe **Starlix** either by itself or together with metformin if one medicine alone is not sufficient to control your blood sugar levels.

How to take Starlix

The tablets should be swallowed whole with a glass of water.

When to take Starlix

Starlix is best taken immediately before a main meal (1 minute) but can be taken at any time in the 30 minutes before starting the meal.

If you have to skip a main meal, do not take the corresponding dose of **Starlix**.

How long to take Starlix

Take **Starlix** daily before main meals as long as recommended by your doctor.

If you take more Starlix than you should

Seek medical advice if you have accidentally taken too many tablets. If you experience symptoms of low blood sugar – e.g. you feel dizzy, light-headed, hungry, nervous and shaky, drowsy, confused and/or sweaty – you should eat or drink something containing sugar.

Call for urgent medical assistance – or make sure that someone else does this for you - if you feel as if you are about to suffer a severe hypoglycemic episode (loss of consciousness, seizure).

If you forget to take Starlix

If you forget to take a tablet simply skip that dose and take the next one before your next meal.

Do not take a double dose of **Starlix** to make up for the one that you missed.

Possible side effects

Like all medicines, **Starlix** can have side effects. The side effects caused by **Starlix** are usually mild to moderate.

The most common side effects are symptoms of low blood sugar (hypoglycemia) which are usually mild. These symptoms include sweating, dizziness, shaking, weakness, hunger, palpitations (perceivable and fast heart beat), tiredness and nausea. It can also be caused by

lack of food or too high a dose of any antidiabetic medicine you are taking. If you experience symptoms of low blood sugar, you should eat or drink something containing sugar.

Rare cases of abnormalities in liver function tests and allergic (hypersensitivity) reactions such as rash and itching were reported.

Inform your doctor or pharmacist if you notice any other side effects not mentioned in this leaflet.

Storing Starlix

Keep **Starlix** out of the reach and sight of children.

Store in the original package.

Store **Starlix** between 15-30°C.

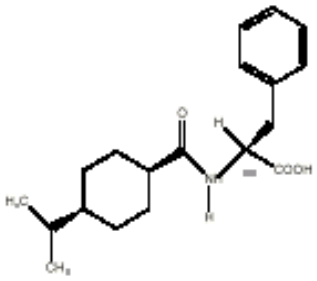
Do not use **Starlix** after the expiry date shown on the pack.

Do not use any **Starlix** pack that is damaged or shows signs of tampering.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: nateglinide
Chemical Name: [N-[trans-4-isopropylcyclohexylcarbonyl]-D-phenylalanine]
Structural Formula:



Molecular Formula: $C_{19}H_{27}NO_3$

Molecular Weight: 317.43

Physical Form: White crystalline powder

Solubility: Freely soluble in methanol, ethanol and in chloroform, soluble in ethylether, sparingly soluble in acetonitrile and in octanol, and practically insoluble in water.

pK_a values: pK_a=3.1

Melting Point: 138.9^0C

COMPOSITION OF DRUG PRODUCT

Starlix film-coated tablets contain the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide (red or yellow), lactose (hydrous), magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc and titanium dioxide.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15-30°C. Keep bottles tightly closed.

AVAILABILITY OF DOSAGE FORM

Starlix (nateglinide) 60 mg tablets are pink, round, beveled edge with "**Starlix**" debossed on one side and "60" on the other side. Available in bottles of 100, 500 and 1000 and in cartons containing 1 and 7 blister strips of 12 tablets.

Starlix (nateglinide) 120 mg tablets are yellow, ovaloid with "**Starlix**" debossed on one side and "120" on the other side. Available in bottles of 100, 500, and 1000 and in cartons containing 1 and 7 blister strips of 12 tablets.

Starlix (nateglinide) 180 mg tablets are red, ovaloid with "**Starlix**" debossed on one side and "180" on the other side. Available in bottles of 100, 500, and 1000 and in cartons containing 1 and 7 blister strips of 12 tablets.

PHARMACOLOGY

In animal models the rapid, transient and glucose dependent nature of the insulinotropic action of nateglinide markedly reduces mealtime glucose excursions while minimizing total insulin exposure and hypoglycemic potential. Chronic studies in animal models have demonstrated that nateglinide preserved pancreatic insulin content and had long-term efficacy in controlling mealtime glucose excursions when compared to long acting insulinotropic agents and placebo.

TOXICOLOGY

Acute Toxicity

The acute toxicity of nateglinide was assessed orally in rats and dogs, and following i.v. injection in mice and dogs. The results are summarized in the following Table:

Single dose toxicity studies

Species	Route	Dose (mg/kg)	Major findings
Mouse	iv	100 – 400	$LD_{50} \approx$ 200-400 mg/kg
Rat	oral (gavage)	500 - 2000	LD_{50} > 2000 mg/kg
Dog	oral (capsule)	100 - 2000	LD_{50} > 2000 mg/kg

Nateglinide showed low acute toxic potential. No lethality was observed after single oral doses up to 2000 mg/kg in either rats or dogs. Intravenous administration to mice caused tonic convulsions (=200 mg/kg) and death at 400 mg/kg.

The low acute toxicity indicates that there is a minimal risk of intoxication following accidental or deliberate overdosing.

LONG TERM TOXICITY STUDIES

Species	Route	Duration	Dose (mg/kg)	Major findings
Mouse	oral (diet)	13 weeks	0.5, 1, 2%*	NTEL = 0.5% Decreased body weight gain and low packed cell volume at 1 and 2%.
Rat	oral (diet)	13 weeks	5000, 10000, 20000 ppm**	All doses: decreased body weight gain. 20000 ppm: small increase in ALT No NOEL
Rat	oral (diet)	13 weeks	625, 1250, 2500 ppm***	NOEL = 2500 ppm
Rat	oral (gavage)	13 weeks	100, 300, 1000, 2000	NTEL = 100 mg/kg ≥1000 mg/kg: Stomach erosions/ulcers 2000 mg/kg: mortality (terminated on day 10)
Rat	oral (gavage)	52 weeks	30, 100, 500	NTEL = 100 mg/kg 500 mg/kg: Stomach erosions/ulcers
Rat	i.v.	5 days	6, 24, 48	48 mg/kg: Local irritation and necrosis at injection site.
Rat	i.v.	2 weeks	6, 24	NTEL = 24 mg/kg; necrosis at injection site.
Dog	oral (capsule)	13 weeks	10, 30, 100, 300	NOEL = 30 mg/kg 300 mg/kg: Mortality, increased ALT, AST, bilirubin. Bile plugs in liver; ulceration of duodenum, erosion of stomach.
Dog	oral (capsule)	up to 13 weeks, + up to 5 weeks recovery	300	Elevated ALT, AST, ALP, total bilirubin. Yellowish change in organs, tissues & subcutis. Deposition of brown pigment in hepatocytes and hypertrophy of zona fasciculata in adrenals. Reversible single cell necrosis, fat deposition and cytoplasmic degeneration of hepatocytes, atrophy and ulcer of gallbladder mucosa, duodenal ulcers.
Dog	oral (capsule)	12 months	10, 30, 100	NTEL = 100 mg/kg
Dog	i.v.	acute and 5 days	5, 10, 20 (single dose) 20 (5 days)	MTD not achieved.
Dog	i.v.	2 weeks	4, 20	NTEL = 20 mg/kg; inflammatory lesions at injection site.

* 0.5, 1, 2% = 981/1352, 2643/2944, 6145/7067 mg/kg for males/females, respectively
** 5000, 10000, 20000 ppm = 364/438, 724/844, 1522/1817 mg/kg for males/females, respectively
*** 625, 1250, 2500 ppm = 52/58, 103/119, 201/240 mg/kg for males/females, respectively

CARCINOGENICITY

Study type	Species/strain	Route	Dose	Comments
104 week carcinogenicity	Mouse/ B6C3F1	Oral (diet)	0.1, 0.3, 1.0% * weeks 1-23 0.03, 0.1, 0.3% ** week 24 to termination	Dose levels of all groups were decreased in week 24 due to decreased body weight gain. At 0.3/0.1% and 1.0/0.3%: increased mortality and peripheral neuropathy in females No tumorigenic response
104 week carcinogenicity	Rat/Crl: CD(SD) BR	Oral (diet)	625, 1250, 2500 ppm***	At 2500 ppm: Slight increase in benign pancreatic islet cell tumors in females.
104 week carcinogenicity	Rat/Crl: CD(SD) BR	Oral (diet)	100, 300, 600, 900 mg/kg	No tumorigenic response.

* Equivalent to 178/233, 535/690, 1991/2552 mg/kg in males/females
** Equivalent to 37/36, 124/123, 390/409 mg/kg in males/females
*** Equivalent to 29/40, 58/79, 117/165 mg/kg in males/females

No evidence of a tumorigenic response was found when nateglinide was administered for 104 weeks to mice at doses up to 400 mg/kg/day or to rats at doses up to 900 mg/kg/day (4.5 and 21 times the maximum recommended human dose in mice and rats, respectively, when compared on the basis of body surface area).

Mutagenesis

Nateglinide was not genotoxic in a variety of *in vitro* (Ames test mouse lymphoma assay, and chromosome aberration assays in Chinese hamster lung cells and V79 cells and i*n vivo* (mouse micronucleus) tests.

REPRODUCTION AND TERATOLOGY

Reproductive function

Study type	Species	Route	Dose (mg/kg)	Major findings
Fertility Studies – Segment 1 Studies				
Segment I	Rat	Oral (gavage)	100, 300, 600	No effect on fertility or reproductive function
Segment II pilot	Rat	Oral (gavage)	100, 300, 1000	No maternal or fetal toxicity
Embryo Toxicity Studies – Segment 2				
Segment II	Rat	Oral (gavage)	100, 300, 1000	No embryotoxicity. No teratogenicity
Segment II range-finding	Rabbit	Oral (gavage)	250, 500, 1000	1000 mg/kg: severe maternal toxicity
Segment II	Rabbit	Oral (gavage)	50, 150, 500	500 mg/kg: maternal and embryo toxicity; gallbladder agenesis NOEL = 150 mg/kg
Supplementary study on fetal gall bladder	Rabbit	Oral (gavage)	300, 500	300 mg/kg: gallbladder agenesis in 5 fetuses from 1 dam; no bile duct abnormalities in these fetuses 500 mg/kg: 11/20 dams died; no live fetuses
Perinatal and Postnatal Studies				
Segment III	Rat	Oral (gavage)	100, 300, 1000	1000 mg/kg: ↓ fetal body weight during lactation. No effect on development or reproductive function.

Fertility was unaffected by administration of nateglinide to rats at doses up to 600 mg/kg (13.5 and 11.4 times the maximum daily human dose in male and female rats respectively, when compared on the basis of body surface area.

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