

PRESCRIBING INFORMATION

Pr **STARLIX***
(nateglinide)
60, 120 and 180 mg Tablets

Therapeutic Classification

Oral Antidiabetic Agent

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 β -cells. Electrophysiologic studies demonstrate that nateglinide has > 300-fold selectivity for pancreatic β -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 α_1 acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1-10 $\mu\text{g/mL}$.

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 P₄₅₀ isoenzyme CYP2C9 (70%) and to a lesser extent by CYP3A4 (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 ¹⁴C-nateglinide is recovered in the urine. Most of the ¹⁴C-nateglinide (83%) is excreted in the urine with an additional 10% eliminated in the feces. Approximately 16% of the ¹⁴C-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 m² or 15-50 mL/min/1.73m²), 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.

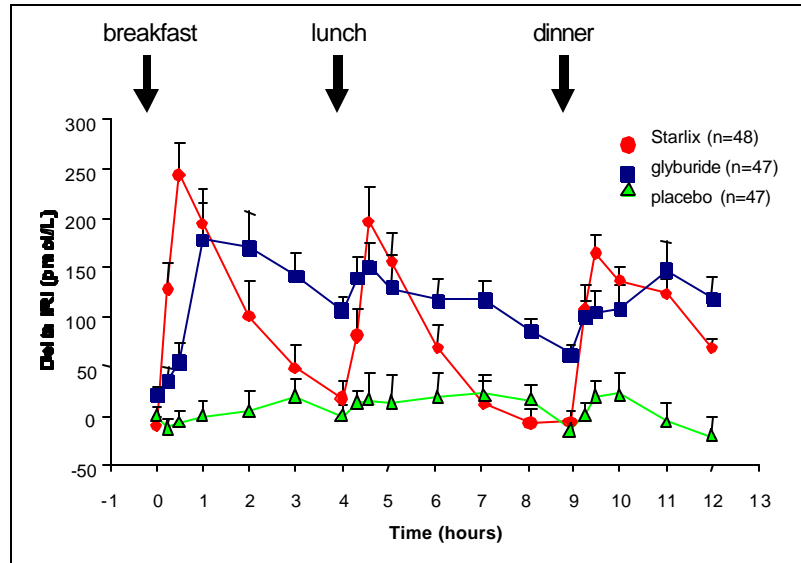
A total of 2122 patients with Type 2 diabetes were treated with **Starlix** in double-blind, placebo or active-controlled studies. These studies included two 24-week placebo controlled studies, two 24-week active controlled studies, and five additional efficacy studies with treatment durations of 8 weeks (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 $AUC_{(0-130 \text{ min})}$. 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 HbA_{1c} 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 C_{max} 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, nifedipine, 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, nifedipine, 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 β -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 near 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.

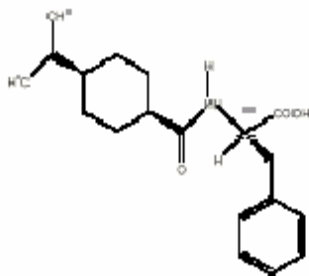
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name : nateglinide

Chemical Name : [N-[trans-4-isopropylcyclohexylcarbonyl]-D-phenylalanine]

Structural Formula:



Molecular Formula: C₁₉H₂₇NO₃

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 °C

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 cartons containing 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 cartons containing 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 cartons containing 7 blister strips of 12 tablets.

Novartis Pharmaceuticals Canada Inc.
Dorval, Québec H9S 1A9

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