Starlix®

Oral blood glucose lowering drug

DESCRIPTION AND COMPOSITION

The active substance is nateglinide.

Each film-coated tablet contains 60 mg or 120 nateglinide.

Active moiety
Nateglinide

60 mg pink, round, bevelled-edge tablet with "Starlix" debossed on one side and "60" on the other.

120 mg yellow, ovaloid tablet with "Starlix" debossed on one side and "120" on the other.

INDICATIONS

Treatment of patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet and physical exercise.

Starlix can be used as monotherapy or in combination with metformin or a thiazolidinedione.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

Starlix 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. If a dose is missed, the next dose should be taken as usual and not to be doubled.

Monotherapy

The usual dose is 120 mg three times daily before meals.

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

In clinical studies, Starlix was administered before main meals, usually breakfast, lunch and dinner.

Combination therapy

Starlix can be used in combination with metformin or thiazolinedione.

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. $HbA_{1c} < 7.5$ %), Starlix 60 mg before meals may be sufficient.

The recommended starting and maintenance dose of Starlix, in combination with thiazolidinedione, is 120mg three times daily before meals.

Special populations

Geriatric patients (patients 65 years of age and older)

No difference has been observed in the safety and efficacy profile of Starlix between the elderly and the general population. In addition, age did not influence the pharmacokinetic properties of Starlix. Therefore no special dose adjustments are necessary for elderly patients (see section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

The safety and efficacy of Starlix have not been evaluated in pediatric patients. Therefore, Starlix is not recommended in this population.

Hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic disease. The systemic availability and the half-life of Starlix in non-diabetic subjects with mild to moderate hepatic impairment do not differ to a clinically significant degree from those in healthy subjects. Patients with severe hepatic impairment were not studied, and Starlix is not recommended for use in this group (see section CLINICAL PHARMACOLOGY).

Renal impairment

No dose adjustment is necessary in patients with renal impairment. The systemic availability and the half-life of Starlix in diabetic subjects with moderate to severe renal impairment (creatinine clearance 15-50 mL/min/1.73 m2) and in patients requiring dialysis do not differ to a clinically significant degree from those in healthy subjects (see section CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Starlix is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients
- Type 1 diabetes
- Diabetic ketoacidosis
- Pregnancy and breast-feeding (see section WOMEN OF CHILD BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY)

WARNINGS AND PRECAUTIONS

Hypoglycemia has been observed in patients with type 2 diabetes on diet and exercise, and in those treated with Starlix (see section ADVERSE DRUG REACTIONS). Elderly, malnourished patients and patients with adrenal or pituitary insufficiency or severe renal impairment (see section CLINICAL PHARMACOLOGY) are more susceptible to the glucose-lowering effect of Starlix treatment. The risk of hypoglycemia in type 2 diabetic patients may be increased by strenuous physical exercise, ingestion of alcohol or insufficient caloric intake on an acute or chronic basis.

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

Hypoglycemia may be difficult to recognize in subjects receiving beta-blockers.

When a patient stabilized on Starlix is exposed to stress such as fever, trauma, infection or surgery, a loss of glycemic control may occur. At such times, it may be necessary to discontinue Starlix treatment and replace it with insulin on a temporary basis.

INTERACTIONS

Effects of nateglinide on other drugs:

Data available from both in vitro and in vivo experiments indicate that nateglinide is predominantly metabolized by the cytochrome P450 enzyme CYP 2C9 (70%) and to a lesser extent by CYP 3A4 (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. Overall, these findings suggest a low potential for clinically significant pharmacokinetic drug interactions.

Nateglinide has no clinically relevant effect on the pharmacokinetic properties of warfarin (a substrate for CYP 3A4 and CYP 2C9), diclofenac (a substrate for CYP 2C9), or digoxin. Thus, no dosage adjustment is required for digoxin, warfarin or diclofenac upon coadministration with Starlix. Similarly, there was no clinically significant pharmacokinetic interaction of Starlix with other oral antidiabetic agents such as metformin or glibenclamide.

Effects of other drugs on nateglinide

In an interaction study 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. *While a more prolonged effect with concomitant administration of CYP2C9 inhibitors (such as voriconazole and sulfinpyrazone) cannot be excluded, the effect is likely to cause hypoglycemia with potent CYP2C9 inhibitors such as fluconazole or in patients known to be poor metabolizers (CYP2C9*3/*3 genotype) of substrates of CYP2C9 enzyme.*

Nateglinide is highly bound to plasma proteins (98%), mainly albumin. *In vitro* displacement studies with highly protein-bound drugs such as furosemide, propranolol, captopril, nicardipine, pravastatin, glibenclamide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide and metformin show 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 and tolbutamide.

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

The hypoglycemic action of oral anti-diabetic agents may be potentiated by certain drugs, including non-steroidal anti-inflammatory agents, salicylates, monoamine oxidase inhibitors, non-selective beta-adrenergic-blocking agents, anabolic hormones (eg. methandrostenolone), guanethidine, gymnema sylvestre, glucomannan and thioctic acid.

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

The hypoglycemic action of oral anti-diabetic agents may be reduced by certain drugs, including thiazides, corticosteroids, thyroid products sympathomimetics, somatropin, somatostatin analogs (eg. lanreotide, octreotide), rifampin, phenytoin and St John’s wort.

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

PREGNANCY, LACTATION, FEMALES, AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

There is insufficient experience in pregnant women, therefore the safety of Starlix in pregnant women cannot be assessed. Starlix must not be used in pregnancy.

The effect of nateglinide on labor and delivery in humans is not known.

Animal data

Nateglinide was not teratogenic in rats at doses up to 1000 mg/kg/day. In rabbits, embryonic development was adversely affected at 500 mg/kg/day and the incidence of gallbladder agenesis or small gallbladder was increased at doses of 300 and 500 mg/kg/day (approximately 24 and 28 times the human therapeutic exposure with a maximum recommended nateglinide dose of 180 mg, three times daily before meals). No such effects were observed at 150 mg/kg/day (approximately 17 times the human therapeutic exposure). Studies in rats have shown no effect on parturition at doses up to 1000 mg/kg/day. During the postnatal period, body weights were lower in offspring of rats administered nateglinide at 1000 mg/kg/day (approximately 40 times the human therapeutic exposure).

Lactation

Nateglinide is excreted in the milk following a peroral dose to lactating rats. At high doses body weights were lower in offspring of rats during the post-natal period (see section NON-CLINICAL SAFETY DATA). Although it is not known whether nateglinide is excreted in human milk, the potential for hypoglycemia in breast-fed infants may exist and therefore nateglinide must not be used in breast-feeding women.

Females and males of reproductive potential

Women of child-bearing potential should take effective contraceptive measures during treatment with Starlix.

Infertility

Nateglinide did not impair fertility in male or female rats (see section NON-CLINICAL SAFETY DATA).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving or operating machinery.

ADVERSE DRUG REACTIONS

Adverse drug reactions (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category, using the following convention

(CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000).

As with other antidiabetic agents, symptoms suggestive of hypoglycemia 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. Symptomatic events confirmed by low blood glucose (plasma glucose < 3.3 mmol/L) were reported in 2.4% of patients in clinical studies.

Table 1 Adverse drug reactions

Immune system disorders	
Rare:	Drug hypersensitivity (including rash, pruritus, urticaria).
Metabolism and nutrition disorders	
Common:	Hypoglycemia (including palpitations, nausea, asthenia, fatigue, increased appetite, dizziness, tremor, hyperhydrosis).
Investigations	
Rare:	Hepatic enzymes increased.

Other events

Most other frequently occurring adverse events in clinical studies were of a similar incidence in Starlix-treated and placebo-treated patients. They include gastrointestinal complaints (e.g. abdominal pain, dyspepsia, diarrhoea), headache, and events consistent with concomitant conditions likely to be present in these patient populations such as respiratory infections.

OVERDOSAGE

In a clinical study in patients, Starlix was administered in increasing doses up to 720 mg a day for 7 days and was tolerated well. There is no experience of an overdose of Starlix in clinical studies. 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.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC code

Other oral blood glucose lowering drugs: A10BX03

Pharmacodynamics (PD)

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

Early insulin secretion is an essential mechanism for the maintenance of normal glycemic control. Nateglinide, when taken before a meal, 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 interaction with

the K^+_{ATP} channel on pancreatic beta-cells. Electrophysiological studies demonstrate that nateglinide has greater than 300-fold selectivity for pancreatic beta-cell versus cardiovascular K^+_{ATP} channels.

Unlike other oral anti-diabetic agents, nateglinide induces significant insulin secretion within the first 15 minutes following a meal. This blunts post-meal glucose excursions (peaks). Insulin levels return to baseline within 3 to 4 hours, reducing post-meal hyperinsulinaemia which has been associated with delayed hypoglycemia. Nateglinide is rapidly eliminated.

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 a clear enhancement of insulin secretion. The decreased potential for Starlix to stimulate insulin secretion at lower ambient glucose concentrations provides additional protection from hypoglycemia, such as when a meal is missed.

Pharmacokinetics (PK)

Absorption

Nateglinide is rapidly absorbed following oral administration of Starlix 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 Starlix 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}. The t_{max} was dose independent.

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 (97-99 %) bound 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 0.1to 10 μg Starlix/mL.

Metabolism

Nateglinide is extensively metabolized by the mixed-function oxidase system prior to elimination. 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 isoprene 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 metabolized by the cytochrome P450 enzyme CYP2C9 (70 %) and to a lesser extent by CYP3A4 (30 %).

Elimination

Nateglinide and its metabolites are rapidly and completely eliminated. Approximately 75% of the administered [14C] nateglinide is recovered 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 to 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 Starlix 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.

Special populations

Geriatric patients (patients 65 years of age and older)

Age did not influence the pharmacokinetic properties of Starlix (see section DOSAGE AND ADMINISTRATION).

Renal impairment

Average exposure (AUC (0-24)), peak plasma concentration (Cmax) and apparent body clearance in moderate/severe renal impairment (creatinine clearance 15-50 ml/min/1.73 m2) patients with diabetes (type 1 and 2) were comparable to that of healthy subjects. There was no significant change in exposure of nateglinide in patients on hemodialysis, however peak plasma concentration (Cmax) decreased by 49%. No correlation was found between exposure of nateglinide and renal function, as measured by creatinine clearance (CrCL) in moderate/severe renal impairment patients (see section DOSAGE AND ADMINISTRATION).

Repeated dosing with 90 mg once daily for 1 to 3 months in diabetic patients with end-stage renal disease (ESRD) showed pronounced M1 metabolite accumulation up to 1.2 ng/mL despite the reduced dose. M1 concentration decreased markedly after hemodialysis. Although M1 metabolites show only slight hypoglycemic activity (approximately 5 times lower than nateglinide), metabolite accumulation might increase the hypoglycemic effect of the administered dose.

Hepatic impairment

Nateglinide exposure in patients with mild/moderate hepatic impairment did not correlate with the degree of hepatic impairment although the average increase in $AUC_{(0-24)}$ was 30% and Cmax was 37% compared to healthy subjects. Apparent body clearance was decreased by 8%. These differences were not statistically significant. The pharmacokinetics of nateglinide, have not been evaluated in patients with severe hepatic impairment, and nateglinide is therefore not recommended in these patients (see section DOSAGE AND ADMINISTRATION).

Food effect

When given post-prandially, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in Cmax and a delay in time to peak plasma concentration (t_{max}). It is recommended that Starlix 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.

Gender

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

CLINICAL STUDIES

In clinical studies, treatment with Starlix as monotherapy resulted in an improvement in glycaemic control as measured by HbA1c and post-meal glucose. In combination with metformin, which mainly affected fasting plasma glucose, the effect on HbA1c was synergistic compared to either agent alone due to the complementary mode of action of the substances.

In a 24-week study, patients who were stabilized with high-dose sulphonylureas for at least 3

months and directly switched to monotherapy with Starlix experienced reduced glycemic control, as evidenced by increases in FPG and HbA_{1c}. Combination of Starlix with sulphonylureas and switching from sulphonylureas to Starlix monotherapy cannot be recommended.

NON-CLINICAL SAFETY DATA

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and effects on fertility.

Mutagenicity

Nateglinide was not genotoxic in the in vitro Ames test, mouse lymphoma assay, chromosome aberration assay in Chinese hamster lung cells, or in the in vivo mouse micronucleus test.

Carcinogenicity

No evidence of a tumorigenic response was observed when nateglinide was administered for 104 weeks to mice at doses up to approximately 400 mg/kg/day or to rats at doses up to 900 mg/kg/day.

Reproduction toxicity

(see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Fertility

Fertility was unaffected by administration of nateglinide to rats at doses up to 600 mg/kg/day.

EXCIPIENTS

Lactose monohydrate, cellulose microcrystalline, povidone, croscarmellose sodium, magnesium stearate, iron oxides (red or yellow, E172), hypromellose, titanium dioxide (E171), talc, macrogol, silica, colloidal anhydrous.

Pharmaceutical formulations may vary between countries.

INCOMPATIBILITIES

Not applicable.

STORAGE

Starlix must not be used after the date marked “EXP” on the pack.

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

Information might differ in some countries.

Nateglinide must be kept out of the sight and reach of children.

INSTRUCTIONS FOR USE AND HANDLING

Note: Starlix should be kept out of the reach and sight of children

Manufacturer:

See folding box.

International Package Leaflet

Information issued: August 2017.SIN

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