Summary of Product Characteristics for Pharmaceutical Products

1. NAME OF THE MEDICINAL PRODUCT

EuNat (Nateglinide USP) 60 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains; 60 mg nateglinide.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Pink, round, film coated plain on Both Sides

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

The recommended starting dose is 60 mg three times daily before meals, particularly in patients who are near goal HbA1c. This may be increased to 120 mg three times daily.

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

The recommended maximum single daily dose is 180 mg taken before the three main meals. The total maximum daily dose should not exceed 180 mg before three main meals.

Specific patient groups

Elderly

The clinical experience in patients over 75 years of age is limited.

Children and adolescents

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

Patients with hepatic impairment

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

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment.

Although there is a 49 % decrease in C_{max} of nateglinide in dialysis patients, the systemic availability and half-life in diabetic subjects with moderate to severe renal insufficiency (creatinine clearance 15– 50 ml/min) was comparable between renal subjects requiring haemodialysis and healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

Others

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

4.3 Contraindications

Starlix is contraindicated in patients with:

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

4.4 Special warnings and special precautions for use

General

Nateglinide should not be used in monotherapy.

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

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

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

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

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

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

Specific patient groups

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

In vivo, nateglinide has no clinically relevant effect on the pharmacokinetics of medicinal products metabolised by CYP 2C9 and CYP 3A4. The pharmacokinetics of warfarin (a substrate for CYP 3A4 and CYP 2C9), diclofenac (a substrate for CYP 2C9), and digoxin were unaffected by coadministration with nateglinide. Conversely, these medicinal products had no effect on the pharmacokinetics of nateglinide. Thus, no dosage adjustment is required for digoxin, warfarin or other drugs that are CYP 2C9 or CYP 3A4 substrates upon coadministration with Starlix. Similarly, there was no clinically significant pharmacokinetic interaction of Starlix with other oral antidiabetic agents such as metformin or glibenclamide.

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

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Based on the experience with nateglinide and with other hypoglycaemic agents, the following adverse reactions have been seen. Frequencies are defined as: common (> 1/100, < 1/10); uncommon (> 1/1000, < 1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000).

Hypoglycaemia

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

nateglinide+metformin combination, 6.9% with metformin alone, 19.8% with glibenclamide alone, and 4.1% with placebo.

Immune system disorders

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

Metabolism and nutrition disorders

Common: Symptoms suggestive of hypoglycaemia.

Hepato-biliary disorders

Rare: Elevations in liver enzymes.

Other events

Other adverse events observed 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via https://pv.pharmacyboardkenya.org

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Nateglinide is an amino acid (phenylalanine) derivative, which is chemically and pharmacologically distinct from other antidiabetic agents. Nateglinide is a

rapid, short-acting oral insulin secretagogue. Its effect is dependent on functioning beta cells in the pancreas islets.

Early insulin secretion is a mechanism for the maintenance of normal glycaemic control. Nateglinide, when taken before a meal, restores early or first phase insulin secretion, which is lost in patients with type 2 diabetes, resulting in a reduction in post-meal glucose and HbA_{1c}.

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

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

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

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

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

The efficacy of nateglinide in combination with metformin has not been compared to the combination of sulphonylurea plus metformin.

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

5.2 Pharmacokinetic properties

Absorption and bioavailability

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

Distribution

The steady-state volume of distribution of nateglinide based on intravenous data is estimated to be approximately 10 litres. *In vitro* studies show that nateglinide is extensively bound (97-99 %) to serum proteins, mainly serum albumin and to a lesser extent alpha$_1$-acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1-10 µg Starlix/ml.

Metabolism

Nateglinide is extensively metabolised. The main metabolites found in humans result from hydroxylation of the isopropyl side-chain, either on the methine carbon, or one of the methyl groups; activity of the main metabolites is about 5-6 and 3 times less potent than nateglinide, respectively. Minor metabolites identified were a diol, an isopropene and acyl glucuronide(s) of nateglinide; only the isopropene minor metabolite possesses activity, which is almost as potent as nateglinide. Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

Excretion

Nateglinide and its metabolites are rapidly and completely eliminated. Most of the [14C] nateglinide is excreted in the urine (83 %), with an additional 10 % eliminated in the faeces. Approximately 75 % of the administered [^{14}C] nateglinide is recovered in the urine within six hours post-dose. Approximately 6-16 % of the administered dose was excreted in the urine as unchanged drug. Plasma concentrations decline rapidly and the elimination half-life of nateglinide typically averaged 1.5 hours in all studies of 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.

Food effect

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

Sub-populations

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

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

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

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Intragranular Ingredients

Mannitol (Pearlitol 100 SD) USP

Corn Starch 400 L USP-NF

Croscarmellose Sodium USP-NF

Colloidal Silicon Dioxide (Aerosil 200 Pharma) USP-NF

Sodium Lauryl Sulphate USP-NF

Polyvinyl Pyrolidone (Kollidon 30) USP-NF

Purified Water USP

Extragranular Ingredients

Mannitol (Pearltol 200 SD) USP

Sodium Starch Glycolate (Glycolys LV) USP-NF

Pre-Gelatinized Starch (Starch 1500) USP-NF

Purified Talc USP-NF

Sodium Stearyl Fumarate (Alubra PG 100) USP-NF

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6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C.

6.5 Nature and contents of container

Nateglinide tablets USP 60 mg are packed in Aluminium lidding foil and non-toxic Transparent PVC/PE/PVDC film. Such blister will contain 14 tablets. Such 2 blisters will be packed in 300 gsm FBB pre-printed carton to give final pack style 2 x 14 T.

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

CADILA PHARMACEUTICALS LIMITED

Survey No. 1389, Dholka – 387 810, Ahmedabad, Gujarat State

Country: India

8. MARKETING AUTHORISATION NUMBER(S)

H2022/CTD6362/12438

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

26/10/2022

10. DATE OF REVISION OF THE TEXT

26/10/2022