



Nateglinide

Updated: May 21, 2019.

OVERVIEW

Introduction

Nateglinide is an oral hypoglycemic agent and amino acid derivative that stimulates insulin secretion from the pancreas and is used in the therapy of type 2 diabetes. Nateglinide has been linked to rare instances of clinically apparent acute liver injury.

Background

Nateglinide (na teg' li nide) is an insulin secretagogue that is similar in action but different in structure from the sulfonylureas. It is a derivative of phenylalanine and stimulates insulin secretion by blocking ATP sensitive potassium channels in pancreatic beta-cells, causing cell membrane depolarization which results in calcium influx and insulin secretion. Nateglinide has been shown to reduce the postprandial increase in glucose in patients with type 2 diabetes and improve glycemic control. Nateglinide was approved for use in the United States in 2000. The current indications are for management of type 2 diabetes used in combination with diet and exercise, with or without other oral hypoglycemic agents. Nateglinide is available generically and under the brand name Starlix in tablets of 60 and 120 mg. The typical initial dose in adults is 120 mg three times daily before meals. Side effects of nateglinide include diarrhea, nausea, gastrointestinal upset, hypoglycemia, dizziness and rash.

Hepatotoxicity

In several large clinical trials, serum aminotransferase elevations were no more common with nateglinide than with placebo. The enzyme elevations that occurred were asymptomatic and resolved rapidly with stopping therapy. Since its approval and with wide scale use, the FDA and the sponsor have received reports of clinically apparent liver injury attributed to nateglinide. However, none of these cases has been published and the clinical features, time to onset, course and outcome of the injury have not been described. The metiglinide analogue repaglinide has been implicated in rare cases of cholestatic or mixed hepatitis, but whether nateglinide liver injury is similar is not known. Thus, nateglinide is likely to be a very rare cause of clinically apparent liver disease.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of nateglinide induced liver injury is not known, but nateglinide is extensively metabolized by the liver via the P450 system (CYP 2C9 and 3A4), and liver injury may be the result of production of a toxic or immunoreactive intermediate.

Outcome and Management

There is no information on results of rechallenge on cross sensitivity to hepatic damage among the various metiglinides. Reexposure and use of other metiglinides after clinically apparent liver injury related to nateglinide should be done with caution.

References regarding the safety and hepatotoxicity of nateglinide and repaglinide are given with the Overview section on the Metiglinide Analogues (updated June 2018).

Drug Class: [Antidiabetic Agents](#)

Other Drugs in the Subclass [Metiglinide Analogues: Repaglinide](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Nateglinide – Generic, Starlix®

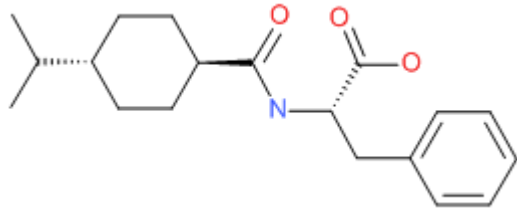
DRUG CLASS

Antidiabetic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Nateglinide	105816-04-4	C ₁₉ H ₂₇ N-O ₃	 The chemical structure of Nateglinide is shown. It consists of a cyclohexane ring substituted with an isopropyl group (dashed bond) and a propionamide group (solid bond). The nitrogen of the propionamide group is further substituted with a 2-phenylethyl group (dashed bond).