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Linagliptin

Updated: January 3, 2018.

OVERVIEW

Introduction

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor which is used in combination with diet and exercise in the therapy of type 2 diabetes, either alone or in combination with other oral hypoglycemic agents. Linagliptin has been linked to rare instances of clinically apparent liver injury.

Background

Linagliptin (lin" a glip' tin) is an inhibitor of dipeptidyl peptidase-4, which is the major enzyme responsible for the degradation of glucagon-like peptide-1 (GLP-1), an important gastrointestinal hormone (incretin) that increases glucose dependent insulin secretion by the pancreas. By prolonging the effect of GLP-1, linagliptin increases insulin levels and lowers blood glucose, thereby improving glycemic control in patients with type 2 diabetes. Linagliptin was approved for use in the United States in 2011 and was the third DPP-4 inhibitor introduced into clinical practice. Its current indications are for management of glycemic control in type 2 diabetes used in combination with diet and exercise, with or without other oral hypoglycemic agents or insulin. Linagliptin is available in tablets of 5 mg under the brand name Tradjenta and in fixed combinations with metformin under the name Jentadueto and with empagliflozin under the name Glyxambi. The typical dose of linagliptin in adults is 5 to 10 mg once daily. Adverse reactions to linagliptin are not common, but may include headache, nausea, allergic reactions and rash. Hypoglycemia is uncommon with linagliptin alone (<1%), but occurs in higher rates when it is combined with other oral hypoglycemic agents. Rare, but potentially severe adverse events reported with linagliptin, as with most DPP-4 inhibitors, include pancreatitis (~0.2%), bullous pemphigoid, severe arthralgias and hypersensitivity reactions.

Hepatotoxicity

In large clinical trials, rates of serum enzyme elevations were similar with linagliptin therapy (<1%) as with placebo, and no instances of clinically apparent liver injury were reported. Nevertheless, postmarketing experience suggests that DPP-4 inhibitors can cause hepatic enzyme elevations as well as rare instances of clinically apparent liver injury. A single case report of liver injury due to linaglitin was published in 2014. The latency to onset was 1 month and the pattern of enzyme elevations hepatocellular without immunoallergic features. Recovery was somewhat delayed and was still incomplete three months later. ANA positivity arose during recovery. Thus, linagliptin like other DPP-4 inhibitors has been linked to rare instances of acute liver injury.

Likelihood score: D (possible rare cause of clinically apparent acute liver injury).

Mechanism of Injury

The cause of possible liver injury during linagliptin therapy is not known. The drug is mostly metabolized by the liver, largely by the cytochrome P450 system (CYP 3A4), and a toxic or immunogenic intermediate of metabolism may be produced that could cause liver injury.

Outcome and Management

The rare instances of liver injury reported with the DPP-4 inhibitors have been self-limited and resolved rapidly with stopping the medication. The similarity in activity among the DPP-4 inhibitors suggests that there may be cross sensitivity to hepatic injury among the different agents, but this has not been reported. However, the other common antidiabetic medications in use should be tolerated without increased risk of liver injury.

References regarding the hepatotoxicity and safety of the DPP-4 inhibitors are given in the Overview section of DPP-4 Inhibitors (updated 03 January 2018).

Drug Class: Antidiabetic Agents, Incretin-Based Drugs

Other Drugs in the Subclass, Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: Alogliptin, Saxagliptin, Sitagliptin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Linagliptin – Tradjenta®

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
Linagliptin	668270-12-0	C25-H28-N8-O2