



Revefenacin

Updated: April 12, 2019.

OVERVIEW

Introduction

Revefenacin is a synthetic anticholinergic agent that is used as a once daily, nebulized inhalant for maintenance treatment of patients with chronic obstructive pulmonary disease. Revefenacin has not been implicated in causing liver enzyme elevations or clinically apparent acute liver injury.

Background

Revefenacin (rev' e fen' a sin) is a synthetic anticholinergic which inhibits the muscarinic actions of acetylcholine on autonomic nerve endings, which decreases bronchial smooth muscle contractions and can alleviate bronchospasm in patients with chronic obstructive pulmonary disease (COPD). Revefenacin has potent activity against muscarinic acetylcholine receptors found in bronchial smooth muscle (M3). Its quaternary ammonium structure decreases its ability to cross lipid membranes such as the blood brain barrier. Revefenacin was approved for use in the United States in 2018 for use as a once daily respiratory inhalant for maintenance treatment of bronchospasm associated with COPD. Revefenacin is available under the brand name Yupelri as an inhalation solution in multiuse vials of 175 mcg in 3 mL. The recommended dose in adults is 175 mcg by inhalation once daily. When given by inhaler, revefenacin has minimal systemic absorption and few anticholinergic side effects. Side effects are mild but can include the headache, cough, symptoms of upper respiratory infections and back pain. Revefenacin is not recommended for patients with hepatic impairment, and concurrent use of other anticholinergic agents should be avoided. Potential severe adverse events include paradoxical bronchospasm, narrow-angle glaucoma, urinary retention and immediate hypersensitivity reactions.

Hepatotoxicity

Like other anticholinergic agents, revefenacin has not been linked to episodes of liver enzyme elevations or clinically apparent liver injury. Another reason for its hepatic safety may relate to its low systemic absorption when administered by inhaler.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Drug Class: [Anticholinergic Agents](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Revefenacin – Yupelri®

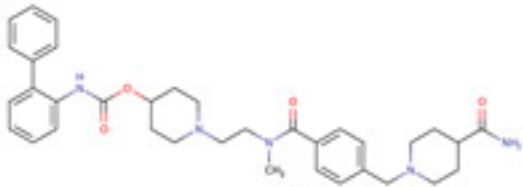
DRUG CLASS

Anticholinergic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Revefenacin	864750-70-9	C35-H43-N5-O4	 <p>The chemical structure of Revefenacin is a complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected via an amide bond to a biphenyl group. The other nitrogen is connected via an ether linkage to another piperazine ring. This second piperazine ring is further connected via a secondary amine to a benzamide group, which is in turn connected to a third piperazine ring. The third piperazine ring has a methyl group on one nitrogen and a primary amide group on the other.</p>

ANNOTATED BIBLIOGRAPHY

References updated: 12 April 2019

Abbreviations: COPD, chronic obstructive pulmonary disease.

Barnes PJ. Pulmonary pharmacology. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 727-49.

(Textbook of pharmacology and therapeutics).

Pudi KK, Barnes CN, Moran EJ, Haumann B, Kerwin E. A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized revefenacin in patients with chronic obstructive pulmonary disease. *Respir Res* 2017; 18: 182. PubMed PMID: 29096627.

(Among 355 patients with chronic obstructive pulmonary disease [COPD] treated with nebulized revefenacin [44, 88, 175, or 350 mcg] or placebo once daily for 28 days, forced expiratory volume improved more with the higher doses than with placebo, and adverse event rates were similar in all groups, systemic anticholinergic effects being uncommon).

Quinn D, Barnes CN, Yates W, Bourdet DL, Moran EJ, Potgieter P, Nicholls A, et al. Pharmacodynamics, pharmacokinetics and safety of revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies. *Pulm Pharmacol Ther* 2018; 48: 71-9. PubMed PMID: 28987804.

(Among 59 patients with COPD treated with once daily nebulized revefenacin or placebo for 7 days, forced expiratory volume improved with all doses of revefenacin compared to placebo, and adverse events were mild and similar in rates in all groups).

Heo YA. Revefenacin: first global approval. *Drugs* 2019; 79: 85-91. PubMed PMID: 30560478.

(Review of the development, clinical efficacy and safety of revefenacin, an inhaled, long acting muscarinic antagonist approved for use in patients with COPD; mentions that the frequency and severity of adverse events were “generally similar across treatment groups”; no mention of ALT elevations or hepatotoxicity).

Revefenacin (Yupelri) for COPD. *Med Lett Drugs Ther* 2019; 61: 14-5. PubMed PMID: 30856160.

(Concise review of the maintenance therapy of COPD and the clinical efficacy, safety and costs of revefenacin shortly after its approval in the US as a once daily nebulized inhalant for the management treatment of patients with COPD; does not mention ALT elevations or hepatotoxicity).

Available at: <https://www.accessdata.fda.gov/scripts/cder/daf/>

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that there were no differences in laboratory test results between revefenacin and comparator arms of pre-licensure clinical trials and the one patient who developed clinically apparent liver injury during revefenacin treatment was found to have pancreatic cancer as a cause of jaundice).

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