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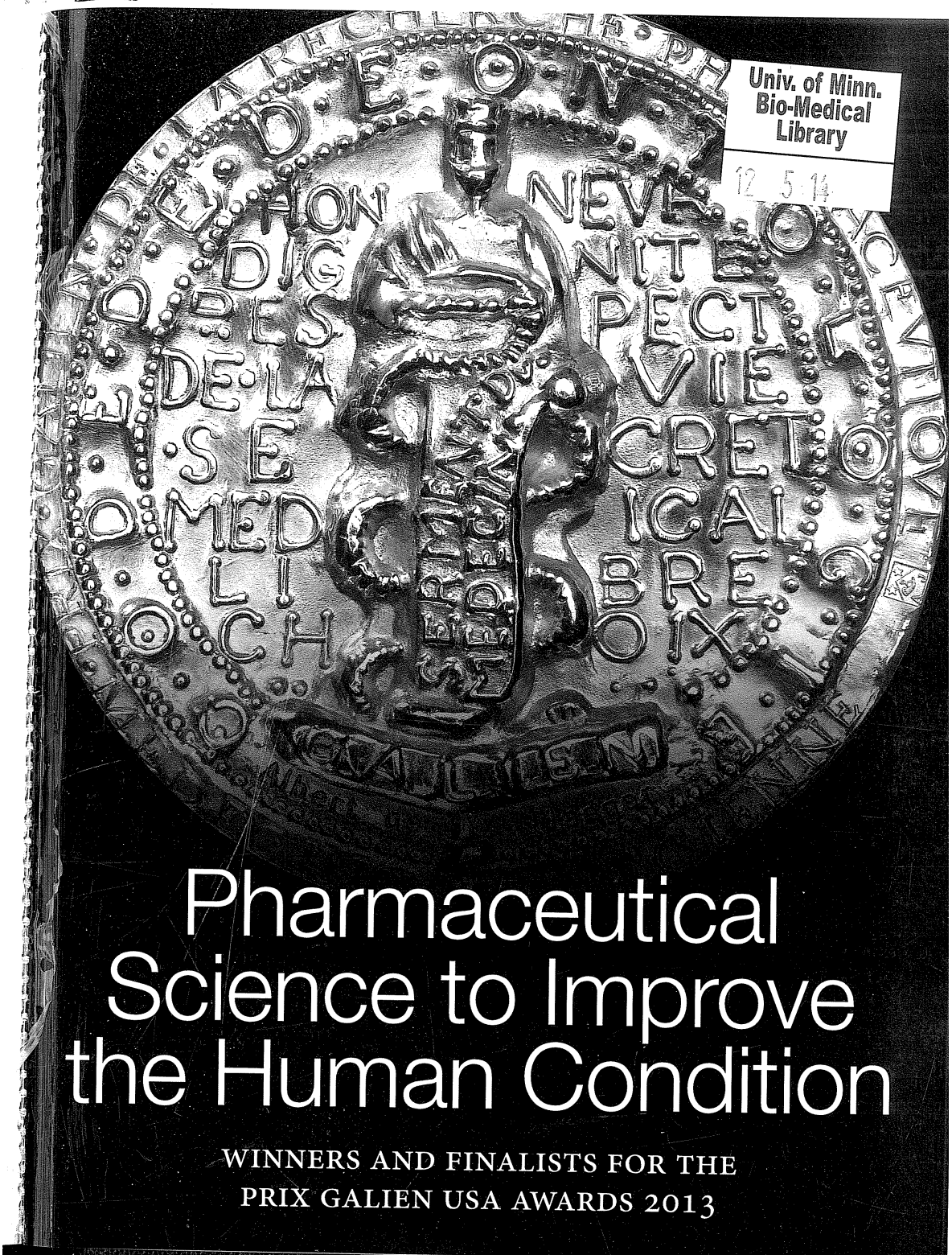

Pharmaceutical Science to Improve the Human Condition

WINNERS AND FINALISTS FOR THE PRIX GALIEN USA AWARDS 2013

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Advances in epilepsy treatment: lacosamide pharmacokinetic profile

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Lacosamide (LCM) is a functionalized amino acid specifically developed for use as an antiepileptic drug (AED) and is currently indicated as adjunctive treatment for partial-onset seizures in adults with focal epilepsy (maximum approved dose 400 mg/day). Characterization of the pharmacokinetic profile is an important aspect in the development of LCM. Studies in healthy subjects and in patients with focal epilepsy have established that LCM has several favorable pharmacokinetic characteristics, including rapid absorption and high oral bioavailability not affected by food, linear and dose-proportional pharmacokinetics, low inter- and intraindividual variability, low plasma protein binding, renal elimination, and a low potential for clinically relevant pharmacokinetic drug–drug interactions both with AEDs and other common medications. Studies have demonstrated bioequivalence among the three LCM formulations (oral tablets, oral solution, and solution for intravenous (IV) infusion), allowing direct conversion to or from oral and IV administration without titration. Thus, the favorable and predictable pharmacokinetic profile and bioequivalence of LCM formulations, coupled with the low potential for clinically relevant pharmacokinetic drug–drug interactions, make LCM an easy-to-use adjunctive treatment for the management of patients with focal epilepsy.

Keywords: lacosamide; pharmacokinetics; drug–drug interactions; focal epilepsy

Introduction

Epilepsy is one of the most common chronic central nervous system disorders, affecting over 65 million people worldwide, 60% of whom are diagnosed with partial-onset seizures.[1–3] Treatment of epilepsy with antiepileptic drugs (AEDs) is aimed at preventing new seizures or reducing the severity of seizures, without decreasing quality of life due to complications from adverse reactions or interactions with other treatments.[2,4] Because epilepsy is a chronic condition, patients frequently require long-term, potentially lifelong treatment with AEDs. A staged approach to the pharmacologic management of patients with AEDs is recommended;[5] however, more than 30% of patients remain uncontrolled and will require AED polytherapy.[6,7] Effective polytherapy requires understanding the metabolic pathways of each AED to avoid the risk of pharmacokinetic drug–drug interactions. Many patients with epilepsy also require pharmacologic treatment for other medical conditions, necessitating an understanding of the potential for pharmacokinetic drug–drug interactions across multiple drug classes.

Selection of an AED is dependent on several patient- and drug-specific factors, some of which are related to the pharmacokinetic properties of the drug, such as dosing frequency, pharmacokinetics, interaction potential, and available formulations.[8–10] Desirable pharmacokinetic characteristics of an AED include rapid and complete oral absorption, linear pharmacokinetics, longer half-life, absence of active metabolites, absence of autoinduction properties, minimal induction or inhibition of principal drug-metabolizing hepatic enzymes, rapid penetration through the blood–brain barrier and entry into the brain, low inter- and intrasubject variability, renal elimination, and low plasma protein binding.[4,11–13]

Every AED has a characteristic pharmacokinetic profile that has been derived from single- and multiple-dose studies in healthy subjects,

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special populations, and in the target population. Limitations of some of the older AEDs include a nonlinear pharmacokinetic profile, high inter- and intraindividual variability, narrow therapeutic window between efficacy and toxicity, or induction (including autoinduction) or inhibition of the drug-metabolizing enzymes.[14] Therefore, while new AEDs are expected to demonstrate comparable efficacy to existing drugs, they also need to have pharmacokinetic properties (i.e., the absorption, distribution, metabolism, and elimination) that make them easy to use with concomitant treatments (AEDs and non-AED drugs) to minimize risk (safety) to patients. Indeed, in terms of overall drug development, concerns surrounding efficacy, safety, and inadequate dosing lead to the failure in obtaining Food and Drug Administration (FDA) approval in 13.2%, 53.8%, and 15.9%, respectively, of first-time new drug applications from the year 2000 to 2012, all of which are related in various ways to the pharmacokinetic characteristics of the drug.[14,15] Thus, characterizing the pharmacokinetic profile of a drug candidate is an important factor in the early phases of AED development.

Lacosamide (LCM; *R*-2-acetamido-*N*-benzyl-3-methoxypropionamide; Vimpat®, UCB Pharma, Brussels, Belgium) is a functionalized amino acid that has been specifically developed as an AED.[16] Functionalized amino acids are amino acid derivatives in which substitutions of specific chemical groups generate a molecule where the *R*-isomer has greater potency than the *S*-isomer.[17,18] LCM is an analogue of D-serine that has amphiphilic properties that allow the molecule to be water soluble enough to be formulated into a parenteral product and lipophilic enough to cross the blood–brain barrier.[17] Preclinical studies have demonstrated that LCM does not affect the sodium channel fast inactivation, a typical mechanism of action of the traditional sodium channel-blocking AEDs.[16,19,20] Instead, LCM acts by selective enhancement of the slow inactivation phase of voltage-gated sodium channels.[19,21] Other potential molecular mechanisms have been reported for LCM, including inhibition of carbonic anhydrase[22] and interaction with the collapsin response mediator protein 2,[23] although the later mechanism remains controversial.[24]

LCM is approved for the adjunctive treatment of partial-onset seizures in patients with epilepsy (aged ≥17 years in the United States,[25] ≥ 16 years in Europe[26]). The recommended initial dose of LCM is 50 mg twice daily (BID; 100 mg/day). The dose may be increased by 100 mg/day in weekly intervals given as two divided doses up to a recommended therapeutic daily dose of 200–400 mg/day, depending on individual patient response and tolerability.[25,26] The efficacy and safety of LCM as adjunctive therapy for adults with focal epilepsy in doses ranging from 200 (100 mg BID) to 600 mg/day (300 mg BID) has been established in multicenter, randomized, placebo-controlled clinical trials.[27–29] Common treatment-emergent adverse events reported in phase 2/3 LCM adjunctive therapy clinical trials (incidence ≥ 10% and greater than placebo) were dizziness, headache, nausea, and diplopia.[25–29]

An overview of the efficacy and safety of LCM from these and other clinical studies has been published in an earlier volume of this journal,[21] but information on pharmacokinetic profile of LCM was limited. This review provides an overview of the clinical pharmacology of LCM, including data on clinical pharmacokinetics and drug–drug interaction studies in healthy subjects and adults with focal epilepsy. The data reviewed in this article will provide the clinician with a fundamental understanding of the development of LCM from a pharmacokinetic perspective, its pharmacokinetic profile in different populations, and the performed drug–drug interaction studies.

General pharmacokinetic overview

Multiple clinical pharmacology studies in healthy subjects (aged 18–87 years) and in patients with focal epilepsy (aged ≥16 years), established the overall absorption, distribution, metabolism, and elimination properties of LCM. Data from these studies have indicated that LCM demonstrates favorable characteristics among AEDs, including a high oral bioavailability,[30,31] linear pharmacokinetic profile,[32,33] dose proportionality with low inter- and intraindividual variability,[31,32] and low potential for clinically relevant pharmacokinetic drug–drug interactions.[34–38] These results are important because they establish the predictable pharmacokinetic profile of LCM and help the clinician shape decisions to achieve the desired drug-response profile.[39]

Absorption

LCM is rapidly and completely absorbed (100% absolute bioavailability) from the gastrointestinal

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