

CONTENTS

REFERENCE JOURNAL
PLEASE CIRCULATE

| | |
|---|-----|
| Tramadol Compared with Diclofenac in Traumatic Musculoskeletal Pain— <i>L. Pagliara, S. Tornago, J. Metastasio, G. Peretti, W. Albisetti, G. Thovez, and C. Ferrari</i> | 473 |
| An Open-Label, Noncomparative, Multicenter Evaluation of Fluconazole with or without Urea Nail Pedicure for Treatment of Onychomycosis— <i>J. E. Fräki, H. T. Heikkila, M. O. Kero, K. E. Kuokkanen, R. O. Oksman, T. T. Rantanen, S. S. Saari, M. L. Sten, S. H. A. Stubb, and P.-E. Uggeldahl</i> | 481 |
| Bioavailability of Once-Daily Venlafaxine Extended Release Compared with the Immediate-Release Formulation in Healthy Adult Volunteers— <i>S. M. Troy, C. Dilea, P. T. Martin, A. S. Rosen, R. J. Fruncillo, and S. T. Chiang</i> | 492 |
| Pharmacokinetics of Once-Daily Venlafaxine Extended Release in Healthy Volunteers— <i>S. M. Troy, C. Dilea, P. T. Martin, C. A. Leister, R. J. Fruncillo, and S. T. Chiang</i> | 504 |
| Effect of Dobutamine on Serum Bile Acid Levels in Patients with Cirrhosis— <i>T. Konno, K. Tada, and K. Akamatsu</i> | 515 |
| Effects of Eicosapentaenoic Acid on Blood Rheology in Rats with Fatty Liver— <i>T. Kurihara, M. Akimoto, M. Tsuchiya, H. Hashimoto, H. Ishiguro, A. Niimi, A. Maeda, M. Shigemoto, K. Yamashita, I. Yokoyama, S. Kashima, and Y. Kikuchi</i> | 525 |
| Sucralfate Prevents Bile Acid-Induced Retardation of Gastric Epithelial Repair in a Rabbit Cultured Cell Model— <i>X.-E. Wang, S. Watanabe, M. Hirose, A. Miyazaki, and N. Sato</i> | 533 |
| Comparative Study of the In Vitro Dose Delivery and Particle Size Distribution Characteristics of an Azmacort Metered-Dose Inhaler in Combination with Four Different Spacer Devices— <i>A. K. Iula, C. L. Flynn, and F. DeLuccia</i> | 544 |

89052691342

Excerpta Medica, Inc.



89052691342

Antibiotics/Infectious Disease

D. Craig Brater, M.D.

Indiana University School of
Medicine

Indianapolis, Indiana
Clinical Pharmacology

Thomas F. Burks, Ph.D.

University of Texas
Houston, Texas
Gastroenterology

Richard Day, M.D.

St. Vincent's Hospital
Sydney Limited
Sydney, Australia

Pharmacology and Toxicology

Marilyn C. Frederiksen, M.D.

Northwestern University Medical
School

Chicago, Illinois
Obstetrics and Gynecology

Curt R. Freed, M.D.

University of Colorado
Health Sciences Center
Denver, Colorado

Clinical Pharmacology/Toxicology

Montreal, Quebec, Canada

Allergy and Immunology

Kenneth Goldblatt, M.D.

The Medical Center at Princeton
Princeton, New Jersey

Pulmonary/Critical Care Medicine

Duncan Hutcheon, M.D.

University of Medicine and
Dentistry of New Jersey

New Jersey Medical School

Newark, New Jersey

Nephrology

Takashi Ishizaki, M.D., Ph.D.

Research Institute

International Medical Center of
Japan

Tokyo, Japan

Clinical Pharmacology

J. Edward Jackson, M.D.

University of California
Medical Center

San Diego, California

Pharmacology

Refer to last page for additional board members.

CURRENT THERAPEUTIC RESEARCH® is cited in the following on-line (and associated in-print) abstracting services: Biological Abstracts (BIOSIS Previews), Current Awareness in Biological Sciences (CABS), Current Contents/Life Sciences and Clinical Medicine, Chemical Abstracts (CA Search and CAS Online), Cambridge Scientific Abstracts (Life Sciences Collection), Current Advances in Clinical Chemistry, SCISEARCH, Excerpta Medica (EMBASE), International Pharmaceutical Abstracts, Medical Documentation Service, PsychInfo, Research Alert, Science Citation Index.

CURRENT THERAPEUTIC RESEARCH®

Clinical and Experimental

Volume 58 Number 8 1997

STATEMENT OF PURPOSE

CURRENT THERAPEUTIC RESEARCH® provides rapid publication of original reports of recent developments in drug therapy. The journal serves an international audience of scientists and clinicians in academia and industry by quickly disseminating research findings through major biomedical databases and encouraging further study.

Results of a broad range of clinical and experimental studies are published monthly. Featured studies run the gamut from pilot studies exploring new drugs and existing drugs for new applications to large multicenter Phase III and IV trials designed to provide strong statistical support to previous efficacy and safety findings.

CURRENT THERAPEUTIC RESEARCH® expects manuscripts to conform to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (the Vancouver style). All manuscripts are peer-reviewed for clinical relevance, technical accuracy, clarity, and objectivity.

Belle Mead, NJ 08502-1510



Trademarks: *CURRENT THERAPEUTIC RESEARCH*® is a registered trademark of Excerpta Medica, Inc.

Publisher: *CURRENT THERAPEUTIC RESEARCH*® (ISSN 0011-393X) (GST #128741063) (IPM #0607851) is published monthly by Excerpta Medica, Inc., a Reed Elsevier Company, with business offices at 105 Raider Boulevard, Belle Mead, New Jersey 08502, telephone (908) 874-0548, FAX (908) 874-3250.

Copyright: Copyright 1997 by Excerpta Medica, Inc. All rights reserved under the United States, International and Pan-American Copyright Conventions. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, computer, photocopying, electronic recording or otherwise, without the prior written permission of Excerpta Medica, Inc. The copyright law of the United States (Title 17, U.S.C., as amended) governs the making of photocopies or other reproductions of copyrighted material.

Photocopy Permissions Policy: This publication has been registered with Copyright Clearance Center, Inc. (CCC), 222 Rosewood Drive, Danvers, Massachusetts 01923, telephone (508) 750-8400. Permission is granted for the photocopying of specified articles provided that the base fee is paid directly to CCC (ref. *CURRENT THERAPEUTIC RESEARCH*® ISSN 0011-393X, specifying volume, number, date and title of article). This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising, and promotional purposes, or for creating new collective works.

Opinions: Opinions expressed in articles are those of the authors and do not necessarily reflect those of Excerpta Medica, Inc. or the Editorial Board. Excerpta Medica, Inc. assumes no liability for any material published herein.

Reprints/Translations/Permissions (both U.S. and international): All inquiries or English language reprint orders must be directed to the journal office in Belle Mead, NJ. Clients interest in translations or permissions must get formal written approval from this office. No other persons are authorized to act on our behalf. Contact: Vicki Donoso, telephone (800) 722-3422 or (908) 281-3694, Fax (908)874-3250.

Subscriptions: Subscriptions are U.S. \$125 (\$15 additional for orders outside the U.S. for air-expedited service). Single copies and back issues are U.S. \$15 (\$18 for shipment outside the U.S.). Circulation records are maintained at P.O. Box 3000, Denville, NJ 07834-3000. Subscription inquiries should be addressed to Gail Colihan, *CURRENT THERAPEUTIC RESEARCH*®, 105 Raider Boulevard, Belle Mead, NJ 08502; FAX (908) 874-3250.

Send address changes to: *CURRENT THERAPEUTIC RESEARCH*®, P.O. Box 3000, Denville, NJ 07834-3000.

Manuscripts: Submit manuscripts to *CURRENT THERAPEUTIC RESEARCH*®, 105 Raider Boulevard, Belle Mead, NJ 08502.

Postmaster: Send address corrections to *CURRENT THERAPEUTIC RESEARCH*®, P.O. Box 3000, Denville, NJ 07834-3000. Periodicals postage is paid at Belle Mead, New Jersey.

BIOAVAILABILITY OF ONCE-DAILY VENLAFAXINE EXTENDED
RELEASE COMPARED WITH THE IMMEDIATE-RELEASE
FORMULATION IN HEALTHY ADULT VOLUNTEERS

STEVEN M. TROY,¹ CLIFFORD DILEA,¹ PATRICK T. MARTIN,¹ AMY S. ROSEN,¹
RICHARD J. FRUNCILLO,² AND SOONG T. CHIANG¹

¹Wyeth-Ayerst Research, Philadelphia, and ²Wyeth-Ayerst Research Clinical Pharmacology
Unit, Graduate Hospital, Philadelphia, Pennsylvania

ABSTRACT

Two open-label, randomized, crossover studies, one single- and one multiple-dose, were conducted to assess the relative bioavailability of two formulations of once-daily venlafaxine extended release (XR) 75 and 150 mg compared with the immediate-release (IR) formulation of venlafaxine. Healthy adults (12 men, 12 women) aged 18 to 45 years were enrolled in each study. Frequent blood samples were taken for determination of the plasma concentrations of venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV). In the single-dose study, the 2 × 75-mg XR formulation and the 150-mg XR formulation were bioequivalent with respect to the rate and extent of absorption of venlafaxine and the formation of ODV, and the area under the plasma concentration-time curve (AUC) of both XR formulations and the AUC of the IR formulation also were bioequivalent after normalization for dose. In the multiple-dose study, the three XR formulations were also bioequivalent with respect to the rate and extent of absorption of venlafaxine and formation of ODV, and the AUC of all three XR formulations compared with the AUC of the IR formulation also showed bioequivalence. Overall, the once-daily venlafaxine XR formulations provided the same total exposure (measured by AUC) to both venlafaxine and ODV. Thus it can be predicted that patients will obtain the same response with the XR formulations as with the IR formulations. *Key words:* venlafaxine, bioavailability, extended release, healthy volunteers.

INTRODUCTION

Venlafaxine hydrochloride (hereafter referred to as venlafaxine) is a unique antidepressant that differs structurally from other currently available antidepressants.¹ Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), inhibit the neuronal uptake of norepinephrine, serotonin, and, to a lesser degree, dopamine,^{2,3} but have no monoamine oxidase inhibitory activity and a low affinity for brain musca-

Address correspondence to: Steven M. Troy, MS, Wyeth-Ayerst Research, P.O. Box 42528, Philadelphia, PA 19101.

Received for publication on May 1, 1997. Printed in the U.S.A.
Reproduction in whole or part is not permitted.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.