

## Introduction

# Comparison of the Bioequivalence of Generic Versus Branded Clozapine

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Clozapine, the first atypical antipsychotic, has been marketed as Clozaril for patients with treatment-refractory schizophrenia since 1989. The patent for Clozaril expired in 1998, and 3 generic formulations of clozapine have received U.S. Food and Drug Administration (FDA) approval.

The FDA considers Clozaril (Novartis Pharmaceuticals Corporation) and the 3 generic forms of clozapine manufactured by Zenith Goldline Pharmaceuticals, Mylan Pharmaceutical, and Geneva Pharmaceuticals, which is a subsidiary of Novartis, to be therapeutically equivalent. Because the 2 available generic products (the Geneva Pharmaceuticals clozapine has not yet been marketed) are less expensive than Clozaril, some institutional formularies have switched from Clozaril to a generic product. In addition, state mental health departments are considering how to implement use of the less expensive product without compromising patient safety.

Isolated reports of therapeutic failures in patients who were being changed from Clozaril to generic clozapine led to a symposium including expert psychiatrists and pharmacists for a discussion on the bioequivalence of the branded and generic formulations. The panel consisted of Marvin C. Meyer, Ph.D.; Neal R. Cutler, M.D.; John C. Kluznik, M.D.; and Y. W. Francis Lam, Pharm.D. Dis-

cussants included William M. Glazer, M.D.; Richard Mofsen, M.D.; William Price, M.D.; and Gregory B. Toney, Pharm.D. This supplement, edited by Larry Ereshefsky, Pharm.D., is derived from that meeting.

Dr. Meyer discusses the FDA requirements for the approval of generic drugs and noted that the clozapine bioequivalence studies were performed in healthy volunteers who were given extremely low clozapine doses. Dr. Cutler examines issues surrounding the use of healthy volunteers versus patients in bioequivalence studies of antipsychotics and recommends that such studies be performed in patients with schizophrenia. Dr. Kluznik et al. present data from a clinical randomized crossover study of a switch from Clozaril to Zenith Goldline clozapine. Their findings suggest that it is unlikely that an across-the-board substitution of generic clozapine for Clozaril in formularies will automatically lead to substantial cost savings. Dr. Lam et al. summarize the findings of a steady-state clinical study of the pharmacokinetic and pharmacodynamic effects of clozapine, suggesting that patients who are stable on Clozaril treatment should be carefully monitored when they are switched to generic formulations.

These experts agreed on the need for guidelines for making the transition from Clozaril to generic clozapine and urged that such switches be made on an individual basis. Formulary decisions should include provisions for outcome monitoring. The switch from one formulation to another in stable patients with schizophrenia should only be done under close supervision that includes regular measurement of serum clozapine concentrations and ongoing evaluation of clinical status. Switching to a generic product in a stable patient should be approached as an individual benefit-versus-risk decision and not made simply from a health-system perspective. Starting new patients on generic clozapine treatment is reasonable, provided that switching between generic formulations is controlled.

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