transmission — therapy that is associated with infertility and a greater risk of long-term toxic effects. These complications might have been avoided if such patients had been treated with mechlorethamine. Moreover, it is unknown as yet whether salvage therapy has been successful in all patients who have had a relapse.

Almost 80% of children and adolescents with cancer can be cured with current therapy. Most of the curative treatment regimens are based on chemotherapeutic agents that have been available for decades, but some of these have recently been in short supply. These shortages are likely to have devastating effects on patients with cancer and must be prevented. For many of these agents, no adequate substitute drugs are available. Our results suggest that even promising substitute regimens should be examined carefully before adoption; what might appear to be a suitable alternative regimen may result in an inferior outcome — an intolerable situation for young people with curable diseases.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Withdrawal of Generic Budeprion for Nonbioequivalence
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The Food and Drug Administration (FDA) has completed a head-to-head bioequivalence study of single doses of the generic drug Budeprion XL 300 mg (extended-release bupropion hydrochloride, manufactured by Impax Laboratories and distributed by Teva Pharmaceuticals) and the brand-name drug Wellbutrin XL 300 mg (Biovail). The agency has concluded that Budeprion XL 300 mg cannot be considered therapeutically equivalent to the brand-name product. We at the FDA are therefore changing our bioequivalence recommendations for extended-release bupropion products and have asked other manufacturers of 300-mg extended-release bupropion products to conduct additional bioequivalence studies.

Within a year after gaining approval at the end of 2006, Budeprion XL 300 mg became the subject of intense media coverage describing adverse events in patients being treated for major depressive disorder who had switched to the generic drug from Wellbutrin XL. Approval of Budeprion XL 300 mg was based on the results of a bioequivalence study of Budeprion XL 150 mg and Wellbutrin XL 150 mg, which were extrapolated to the 300-mg product. Our new data provide direct comparative pharmacokinetic analyses of the 300-mg products.

According to current guidance from the FDA Center for Drug Evaluation and Research, conclusions that two drug products are bioequivalent should reflect significant agreement in pharmacokinetic parameters such that the entire 90% confidence interval associated with the generic-to-reference ratio of geometric means should fall within the bioequivalence limits of 80 to 125%. Budeprion XL 300 mg did not meet these criteria in our bioequivalence study, which involved 24 healthy fasting volunteers and used a single-dose crossover design (see graph). The extent of bupropion absorption after the administration of the generic product, as reflected in the area under the curve of the plasma concentrations plotted over time, was 86% of the absorption with the brand-name product (see graph), but the corresponding 90% confidence interval was 77 to 96%. In addition, the mean peak plasma concentration (C\textsubscript{max}) observed after the administration of Budeprion XL 300 mg was only 75% of that observed after the administration of Wellbutrin XL 300 mg (90% confidence interval, 65 to 87). In certain study participants, the C\textsubscript{max} and the area under the plasma-concentration curve for Budeprion XL were less than 40% of the values with Wellbutrin XL. The C\textsubscript{max} values for hydroxybupropion, the major active metabolite of bupropion hydrochloride, also failed to meet the FDA bioequivalence criteria.

The other major difference observed between Budeprion XL and the brand-name product was in the peak plasma concentration of hydroxybupropion, which was 96% of the absorption with Wellbutrin XL. The C\textsubscript{max} and the area under the curve of the plasma concentrations plotted over time were 77% and 90%, respectively, of the values with Wellbutrin XL. In addition, the mean peak plasma concentration (C\textsubscript{max}) of hydroxybupropion observed after the administration of Budeprion XL 300 mg was only 75% of that observed after the administration of Wellbutrin XL 300 mg (90% confidence interval, 65 to 87). In certain study participants, the C\textsubscript{max} and the area under the plasma-concentration curve for Budeprion XL were less than 40% of the values with Wellbutrin XL. The C\textsubscript{max} values for hydroxybupropion, the major active metabolite of bupropion hydrochloride, also failed to meet the FDA bioequivalence criteria.

The other major difference observed between Budeprion XL 300 mg and Wellbutrin XL 150 mg was in the peak plasma concentration of hydroxybupropion, which was 96% of the absorption with Wellbutrin XL. The C\textsubscript{max} and the area under the curve of the plasma concentrations plotted over time were 77% and 90%, respectively, of the values with Wellbutrin XL. In addition, the mean peak plasma concentration (C\textsubscript{max}) of hydroxybupropion observed after the administration of Budeprion XL 300 mg was only 75% of that observed after the administration of Wellbutrin XL 300 mg (90% confidence interval, 65 to 87). In certain study participants, the C\textsubscript{max} and the area under the plasma-concentration curve for Budeprion XL were less than 40% of the values with Wellbutrin XL. The C\textsubscript{max} values for hydroxybupropion, the major active metabolite of bupropion hydrochloride, also failed to meet the FDA bioequivalence criteria.


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Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL) as a Function of Time in 24 Fasting Healthy Volunteers.

300 mg and Wellbutrin XL 300 mg was in the time to peak drug concentration in the blood (T\text{max}) (see graph). Although FDA guidance does not include T\text{max} as a criterion for bioequivalence of bupropion hydrochloride products, the T\text{max} for Budeprion XL (4 hours) is shorter than that for Wellbutrin XL (5 hours). A similar difference in T\text{max} values was also observed in the bioequivalence study of the 150-mg products that was originally used for extrapolation of data for Budeprion XL 300 mg. But because the comparative area-under-the-curve and C\text{max} values for the 150-mg products fell within FDA parameters and were supported by data on the performance of the product in vitro, Budeprion XL 300 mg was approved.

The use of data extrapolation for the approval of Budeprion XL 300 mg should be considered in historical context. When applications for generic versions of Wellbutrin XL 300 mg began to come under FDA review in 2005, more than 11 million prescriptions for the brand-name product were being written each year. Programs to develop generic bupropion products, and the requisite bioequivalence studies, were important for addressing the widespread need for the treatment of major depressive disorder. At the same time, the FDA and sponsors recognized that bupropion conferred a dose-related risk of seizures, which the agency believed warranted a conservative approach to bioequivalence testing of bupropion in healthy volunteers. Bioequivalence studies that used only the lower strength (150 mg) reflected this conservative approach.

After the approval of Budeprion XL, the T\text{max} disparity between Budeprion XL 150 mg and Wellbutrin XL 150 mg remained a source of concern. This concern, along with the reports that began surfacing after initial marketing of Budeprion XL 300 mg, prompted the FDA to recommend, in November 2007, that the sponsor conduct a clinical comparison with the 300-mg product. The FDA believed that the most appropriate population for this study would be patients who had reported a lack of efficacy or unwanted side effects after switching from Wellbutrin XL 300 mg to Budeprion XL 300 mg; the protocol therefore stipulated the enrollment of such patients. By early 2008, the sponsor had begun preparing to conduct the recommended study. Unfortunately, the study was terminated because of an inability to enroll a sufficient number of patients who met the entry criteria.

Given continuing questions about the efficacy of the 300-mg product, the FDA decided to conduct, under its own auspices, the bioequivalence study described here. Because the results indicated that Budeprion XL 300 mg cannot be considered therapeutically equivalent to Wellbutrin XL 300 mg, the FDA requested that the sponsors of Budeprion XL (Impax Laboratories and Teva Pharmaceuticals) voluntarily withdraw the 300-mg version from the market, which they agreed to do.

The results of the FDA-sponsored study have led the agency to review its approach to other 300-mg extended-release generic bupropion products. The agency has determined that direct bioequivalence studies using the 300-mg strength of the brand-name and generic products are appropriate and feasible. Accordingly, the FDA has requested that other makers of generic extended-release bupropion hydrochloride (Anchen, Actavis, Watson, and Mylan) perform bioequivalence studies of their 300-mg products. The agency is also updating its bioequivalence guidance for these products. As new information regarding these products becomes available, the agency will take any appropriate regulatory actions and will inform the public. Patients who are taking the 300-mg strength of generic extended-release bupropion products and have questions about their medication should be encouraged to...
One recent analysis of Medicare billing data for evaluation-and-management services, conducted by the Office of Inspector General (OIG) of the Department of Health and Human Services, showed that between 2001 and 2010, the proportion of claims for lower reimbursement categories decreased while the use of higher-paid categories increased across all visit types. The largest increase reported was in level 5 emergency department (ED) visits (Current Procedural Terminology [CPT] code 99285; average reimbursement, $173) — from 27% to 48% of Medicare discharges (see graph).

Although the report didn’t assess the reasons for higher billing levels, its findings have been amplified by investigative reports in the media suggesting that fraud is the cause. On September 24, 2012, a formal letter from the U.S. Departments of Justice and Health and Human Services to hospital leaders warned of an escalated effort to prevent fraud and abuse and explicitly linked higher bills to “gaming” made possible by new electronic health record (EHR) technology. The OIG report addressed only physician billing, not hospital billing, and the office has initiated further study into usage of all CPT codes. Although it’s possible that “up-coding” facilitated by increasing use of EHRs has contributed to the trend, other causes such as changing demographics, shifting practice patterns, and the ED’s evolving role in the health care system must also be considered.

To explore these potential contributors, I analyzed a nationally representative sample of Medicare ED discharges in the National Hospital Ambulatory Medical Care Surveys, using methods described previously and detailed in the Supplementary Appendix (available with the full text of this article at NEJM.org). Like the OIG report, my analysis excludes the 35% of