letters

Withdrawal of two generic clopidogrel products in Saudi Arabia for non-bioequivalence

To the Editor: Clopidogrel, a P2Y12 platelet inhibitor, is indicated for the treatment of cardiovascular and cerebrovascular events.[1-3] In February 2018, the Saudi Food and Drug Authority (SFDA) announced the withdrawal of two locally approved clopidogrel generic products (Pedovex and Cardlet), secondary to failure in demonstrating bioequivalence to the reference product (Plavix). With this action, the SFDA has reconfirmed that annual post-marketing surveillance is a continuous ongoing process that ensures that all marketed products are up to standards.

Pedovex was withdrawn after retesting in a new bioequivalence study.[4] The retesting was prompted by several lack of efficacy reports received by the SFDA. In its announcement, the SFDA provided no specific information on how much the withdrawn generics deviated from the reference product. However, the reports of reduced efficacy suggested that these generics failed because of low bioavailability.

The withdrawal of these two local clopidogrel generic products attracted the attention of healthcare professionals in Saudi Arabia because of the vital role of clopidogrel in preventing recurrent stroke and heart ischemia. The action undertaken by the SFDA has also generated concerns among healthcare professionals regarding the quality of some generic products in use in Saudi Arabia. To be approved by regulatory agencies, a generic drug needs to be "bioequivalent" to its brand-name counterpart. The criterion for establishing bioequivalence specifies that the 90% confidence interval (CI) for the geometric mean ratio (test:reference) for the area under the curve (AUC) and maximum concentration (C_{max}), lie between 80% and 125%.[5] This criterion is based on the concept that a 20% change in C_{max}/AUC values is clinically acceptable. This range is reasonable for most drugs. However, it might be considered too wide for drugs with a narrow therapeutic index.[6-8] Therefore, some regulatory agencies have set more stringent criteria to establish bioequivalence for drugs with a narrow therapeutic index. For example, the European Medicines Agency (EMA) requires that the 90% CI for the AUC lie between 90% and 112%.[8] Clopidogrel might be considered in this class.[9,10] Several studies have shown that a modest decrease in the AUC value of the active metabolite of clopidogrel could lead to treatment failure, while a higher AUC value could lead to an increased risk of bleeding.[11-15]

Designing a study to establish bioequivalence for clopidogrel generic products is complex. As a prodrug, it requires in vivo biological transformation to yield the active moiety. Furthermore, there is high between-subject variability in its pharmacokinetics. In the case of prodrugs, both the U.S. Food and Drug Administration (FDA) and EMA recommend that the parent drug, not the active metabolite, be measured. The old analytical method is based on measuring the active metabolite whereas the new technique is based on the parent drug. It is important to note that the SFDA bioequivalence study was based on the new analytical method (measurement of the parent drug), while the two withdrawn generic products were initially registered using the old analytical method (measurement of the active metabolite). Currently, the SFDA is reviewing all clopidogrel generic products that were approved based on the old method (measurement of the active metabolite). This is an important step by the SFDA to ensure the quality of clopidogrel generic products because any issues with the absorption of clopidogrel would lead to underexposure and could be associated with severe outcomes such as strokes and myocardial infarctions.

Compliance with Good Manufacturing Process is another issue associated with these products. Once a generic product is approved for use by regulatory agencies, retesting for bioequivalence is usually not mandated. However, there are other measures to confirm the quality of the generic product after approval. Regulatory agencies require companies to perform routine testing, especially for new batch releases. Furthermore, the SFDA has a post-marketing surveillance system that allows healthcare professionals to report issues such as adverse effects and drug quality defects. This system played an important role in the recent events. The SFDA performed the bioequivalence study based on reports from healthcare professionals of a lack of efficacy with the new generics.

Generic medications are gaining acceptance worldwide, primarily because they cost less than their brand-name counterparts. The market for generic drugs is huge. According to IMS Health, in the US alone, unbranded generic drugs accounted for 80% of prescriptions dispensed during the 2013 fiscal year. It is therefore important to maintain the confidence of healthcare providers and patients in generic products. Using generic medications results in savings for patients, payers, and healthcare systems. Many studies have shown that generics can be equal in efficacy to their brand-name counterparts.[16-20]

Maintaining the confidence of the public and healthcare professionals in generic products requires efforts by regulatory agencies and co-operation from healthcare professionals. An important function of a high-performing healthcare system is ensuring equitable access to essential medical products that are of assured quality, safety, efficacy, and cost-effectiveness.[21] Post-marketing analyses of generic medications performed by the SFDA could help increase public confidence in these products.

We applaud the actions undertaken by the SFDA in investigating and subsequently withdrawing these generic products of clopidogrel that failed to demonstrate bioequivalence. These actions should increase the vigilance of healthcare professionals toward medication outcomes and encourage the reporting of any unusual efficacy and safety outcomes to the SFDA. We also encourage academia and the commercial sector to perform post-marketing surveillance studies of generic medications. Such initiatives should further help in ensuring the quality of generic products after approval.

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