



Need for pharmacogenomic information also for generic medications: Recommendation of the European Society of Pharmacogenomics and Theranostics (ESPT)

Clopidogrel as a prototype

As of 2007, PLAVIX (the original brand name of clopidogrel) had been the second top-selling drug in the world and is, presently, prescribed and marketed in nearly 110 countries. Clopidogrel is currently the thienopyridine of choice for dual antiplatelet therapy (in combination with aspirin) in patients with the full spectrum of acute coronary syndrome and in those undergoing percutaneous coronary intervention and stenting. In a plethora of pharmacogenomic studies on PLAVIX, it has been shown that clopidogrel is a prodrug that requires biotransformation to an active metabolite by CYP450 enzymes (mainly CYP2C19) and paraoxonase 1 (PON-1). There is significant inter-individual variability in the response to PLAVIX, with up to 40% of patients being classified as non-responders, poor responders, or resistant to this drug. Pharmacogenomic information on PLAVIX reveals that genetic polymorphisms of CYP enzymes (most commonly CYP2C19*2), PON-1, and also the ABCB 1 transporter contribute to variation in the response of individual patients to the drug. In March 2010, the Food and Drug Administration (FDA) released a “boxed warning” on PLAVIX addressing the need for pharmacogenomic testing (for detecting CYP2C19 loss-of-function polymorphisms) to identify patients’ altered PLAVIX metabolism, and thus their risk for a suboptimal clinical response to this drug. On the basis of an expanding database, and as an approach to the FDA boxed warning, the American College of Cardiology Foundation/American Heart Association-convened writing committee developed an evidence-based guideline, “Recommendations for Practice,” in July 2010. These documents were validated in France in October 2010 and the SmPC (Summary of Product Characteristics) of PLAVIX was updated accordingly by the French regulatory agency (AFSSAPS).

Situation in France

Generic clopidogrel has been available on the market for a few years and is currently produced by several pharmaceutical companies all over the world. In France, for instance, generic versions of clopidogrel have been available since 2009, with some 21 French generic products currently on the market. The majority of generic versions, however, differ from the branded product, PLAVIX, by the salt formulation. Only the generic clopidogrel marked by Zentiva (the

European generics business for the Sanofi group) has the same formulation as PLAVIX. Although this structural difference may potentially have an impact on the pharmacokinetics of clopidogrel, it does not have an effect on the pharmacogenetic conversion to active metabolites. Therefore, the same pharmacogenetic information as in the PLAVIX label should be present in the generic drug. While pharmacogenetic characteristics of PLAVIX have been well documented and are easily accessible, the relevant data for generic clopidogrel is less available. In France, specifically, a recent survey carried out on the pharmacogenomic information included in the drug labels of marketed French generic clopidogrel products found that of 21, only 5 generics provided the prescribers and patients with the applicable pharmacogenomic information.

Call

The ESPT calls for a harmonized and consensus-based approach to an updatable drug labeling of generic versions for pharmacogenomic information, as is the case for the original drug. This requirement is, undoubtedly, not limited to clopidogrel and should be extrapolated to all medications that are marketed as both branded and generic versions.

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