Post-Marketing Hepatic Safety Profile of Ambrisentan in Patients with Pulmonary Arterial Hypertension

McGoon M¹, Peschel T², Pizzuti D², Sager P², Lulofs J³, DeVault A³, Littman M³, Curtis S³
¹Mayo Clinic, Rochester, MN, U.S.A.
²Gilead Sciences Inc., Foster City, CA, U.S.A.
³Gilead Sciences Int., Cambridge, U.K.

Background: Ambrisentan (ABS) is an ETA-selective, propanoic-acid based, endothelin receptor antagonist (ERA) approved for the treatment of patients with pulmonary arterial hypertension (PAH). Some ERA’s have been associated with definite hepatotoxicity. In vitro studies showed that ABS has minimal effects on hepatic transporters compared to bosentan/sitaxsentan, suggesting a possible basis for greater hepatic safety. In 12 week clinical studies, the frequencies of elevated liver transaminases (AST/ALT) > 3 x ULN were 0.8% with ABS versus 2.3% with placebo (N=483) and during long term treatment (mean 2.2 yrs), the time-based incidence of AST/ALT increases was similar over time, suggesting a random, non-drug related causality. In clinical studies, ABS was well tolerated in pts who had previously required discontinuation of bosentan/ sitaxsentan because of AST/ALT increases (N=63).

Methods: Post-marketing hepatic data were assessed from two programs. Firstly, a Risk Evaluation and Mitigation Strategy (REMS), incorporates the use of a targeted education and outreach program for prescribers and patients, and a performance-linked, closed distribution system for dispensing drug. A key element of the REMS is mandatory monthly AST/ALT testing, with follow-up to ensure compliance before prescriptions are refilled. Secondly, “LabSync” is a voluntary program designed to reduce the burden on patients and prescribers, through which monthly blood draws are coordinated and laboratory test results are provided. The REMS and LabSync programs have facilitated the collection and analysis of hepatic safety data for ABS in the post-marketing setting.

Results: Two years of post-marketing data are now available from 6,622 patients treated for a median of 6 months (range 1–24 months) with ABS. The incidence of hepatic adverse events in this closely monitored population is 1.8%, consistent with the background rate; the frequency of reported AST/ALT values > 3 x ULN was 0.4% (27/6,622). LabSync has collected data in 960 patients, with confirmed (>1 occasion or the last measurement) AST/ALT > 3 x ULN in 6 subjects (0.6%). In addition, assessment of individual (anonymized) reports of hepatic adverse events or patient laboratory data from LabSync provided no clear evidence for a causal association with ABS.

Conclusions: Results from clinical trials showed that ABS was not associated with an increased risk of hepatotoxicity, and the current post-marketing data at 2 years confirm this observation.