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Pharmacovigilance in Post-Marketing: Risk Assessment and Reporting Standards

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Abstract

While there has been new targeted drug therapies released into the market over the recent years, pulmonary arterial hypertension (PAH) remains to be a rapidly progressive disease with poor prognosis. Over time the arteries stiffen and tighten subsequently leaving the heart to pump harder to try and provide enough blood to the body. The extra stress of the increased pumping leads to weakening and enlargement of the heart. The endothelin targeted therapy, Letairis (ambrisentan), is an oral tablet proven to improve quality of life in patients suffering from PAH, WHO Group I – functional class II and III by helping the arteries loosen and relax so that blood can flow steadily to the rest of the body. Although Letairis improves the quality of life for patients, there is a known serious risk of teratogenicity for females of reproductive potential. The risk of teratogenicity is so prominent that the Food and Drug Administration (FDA) required Letairis be placed on the risk evaluation and mitigation strategy program (REMS) to continually assess the risks and benefits of the product during post-marketing. In order to prevent and reduce harm in patients, mechanisms for evaluation and monitoring are vital to drug and patient safety.

Keywords: pharmacovigilance, adverse event, pulmonary arterial hypertension, risk evaluation and mitigation strategy, ambrisentan, letairis

I.   **Introduction**

Pulmonary arterial hypertension (PAH) is a rare progressive disease that affects people of all ages, races, and ethnic backgrounds and is caused by the narrowing and/or tightening of the pulmonary arteries, which connect the right side of the heart to the lungs. In many cases, as PAH develops in patients, blood flow through the pulmonary arteries is restricted and the right side of the heart becomes enlarged due to the increased strain of blood being pumped through the lungs and into the rest of the body. PAH is considered a chronic disease which currently lacks a cure. The World Health Organization (WHO) has classified pulmonary hypertension (PH) into 5 groups based on its causes. Group 1 is divided into 2 subgroups: PAH occurring with a known cause (Associated PAH) and PAH occurring without a known cause (Idiopathic PAH). PH Groups 2 to 5 are referred to as "Secondary PH" because the PH is most likely due to a pre-existing condition such as left heart disease, hypoxemia, chronic thrombotic pulmonary hypertension (CTEPH), or multifactorial mechanisms (Humbert, Sitbon, & Simonneau, 2004). Many who suffer from PAH are misdiagnosed or diagnosed (typically at age 50±15 years) after the disease has aggressively progressed to an advanced stage leaving the patient with few options for treatment (Stamm, Risbano, & Mathier, 2011).

During the 1980's, those living with PAH, especially those with idiopathic PAH, were finding that the disease would rapidly progress and lead to heart failure or death and patients would see a 2.8-year median survival rate after initial diagnosis (Humbert et al, 2004). Some of the first few prospective PAH studies during this time period also showed that the actuarial survival rate after diagnosis was 68-77% at 1-year, 40-56% at 3-years, and 22-38% at 5-years respectively (Humbert et al, 2004). The prevalence of PAH has increased over the years to 15-50 cases per million, substantially effecting those of certain high risk groups the most (PAH-

info.com, 2016). Associated and Secondary PAH have a prevalence of 0.5% in patients infected with human immunodeficiency virus (HIV), 2-3.75% in patients with sickle cell disease, and 7-12% in patients with systemic sclerosis (PAH-info.com, 2016). Idiopathic PAH (IPAH) has an incidence rate of 1-2 cases per million however, it is 2 to 4 times more likely to occur in women than in men and is thought to account for at least 40% of PAH cases overall (PAH-info.com, 2016). This IPAH statistic is also supported by the Pulmonary Hypertension Association Registry (PHAR) which lists 39% of those registered since 2015 are characterized as being diagnosed with IPAH (PHAssociation.org, 2016).

The full version of the original paper is on file with the Director of the MPH Program.

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