

Pulmonary Vascular: Pulmonary Hypertension
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AMBRISANTAN RESCUE THERAPY IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION WHO DISCONTINUED BOSENTAN OR SITAXSENTAN DUE TO LIVER FUNCTION ABNORMALITIES

Michael D. McGoon MD^{*} Adaani E. Frost MD Ronald J. Oudiz MD David B. Badesch MD Nazzareno Galie MD Horst Olschewski MD Vallerie V. McLaughlin MD Lewis J. Rubin MD Mayo Clinic, Rochester, MN

PURPOSE: Ambrisentan is a high affinity, propanoic acid-class, ETA-selective endothelin receptor antagonist (ERA) with once-daily oral doses that are 10-100 times lower than sulfonamide-class ERAs for pulmonary arterial hypertension (PAH). Ambrisentan doses of 2.5 and 5 mg once-daily have been shown to improve 6-minute walk distance (6MWD) and delay clinical worsening in a placebo-controlled study of patients with PAH (ARIES-2), with no incidence of serum aminotransferases >3xULN (LFT abnormalities). To further evaluate the safety of ambrisentan, an open-label study was conducted of patients who had previously discontinued bosentan, sitaxsentan, or both therapies due to LFT abnormalities.

METHODS: Patients received 2.5 mg qd ambrisentan for 4 weeks, 5 mg qd ambrisentan for 20 weeks, and 2.5, 5, or 10 mg qd ambrisentan, thereafter. The primary endpoint was the incidence of LFT abnormalities during 12 weeks of therapy that were related to ambrisentan and resulted in discontinuation of drug.

RESULTS: A total of 36 patients who had previously discontinued bosentan (86%), sitaxsentan (6%), or both therapies (8%) due to LFT abnormalities were enrolled. The median duration of ERA therapy prior to discontinuation was 9 weeks. 64% of patients had idiopathic PAH and 36% had PAH associated with other etiologies. After 12 weeks of therapy, no patients had a recurrence of LFT abnormalities that required discontinuation of ambrisentan. One patient had an isolated incidence of LFT abnormalities that resulted in a temporary dose reduction. Patients continued to receive ambrisentan (mean exposure = 32 weeks, maximum exposure = 48 weeks) and no further LFT abnormalities were observed. Adverse events appeared similar to results from previous ambrisentan clinical studies.

CONCLUSION: No significant LFT abnormalities were observed with long-term ambrisentan administration in patients who had previously discontinued bosentan, sitaxsentan, or both therapies due to LFT abnormalities.

CLINICAL IMPLICATIONS: Ambrisentan appears to be a treatment option for patients who have previously discontinued ERA therapy due to LFT abnormalities and may provide an improved risk-to-benefit ratio for ERA therapy in patients with PAH.

DISCLOSURE: Michael McGoon, Consultant fee, speaker bureau, advisory committee, etc. Myogen Inc.; Product/procedure/technique that is considered research and is NOT yet approved for any purpose, ambrisentan.

PHARMACOKINETIC INTERACTION BETWEEN TADALAFIL AND BOSENTAN IN HEALTHY MALE SUBJECTS

Rebecca E. Wrishko PhD^{*} Jasper Dingemans PhD Albert Yu MD Christelle Darstein MSc Diane L. Phillips PhD Malcolm I. Mitchell MD Lilly Research Laboratories - Eli Lilly and Company, Indianapolis, IN

PURPOSE: Tadalafil is an oral phosphodiesterase type 5 (PDE5) inhibitor approved for the treatment of erectile dysfunction and under investigation for the once-daily treatment of pulmonary arterial hypertension (PAH). Since bosentan is an oral, dual endothelin receptor antagonist indicated in the treatment of patients with PAH, this study determined whether pharmacokinetic interactions exist between tadalafil and bosentan.

METHODS: This was an open-label, randomized, three-period crossover pharmacokinetic drug interaction study. Healthy adult males (N=15; 19 to 52 years) received 10 consecutive days of either tadalafil 40 mg once-daily, bosentan 125 mg twice-daily, and the combination of tadalafil and bosentan. Each treatment period was separated by at least a 7-day washout. Serial blood samples were collected on Day 1 and Day 10 for measurement of tadalafil and bosentan plasma concentrations. Standard evaluation methods using point estimates and 90% confidence intervals (CI) determined the extent of any interaction between tadalafil and bosentan. Safety parameters were monitored.

RESULTS: Following 10 days of multiple-dose administration of bosentan and tadalafil, compared to tadalafil alone, the tadalafil equivalent

ratio (90% CI) for AUC_τ was 0.59 (0.55, 0.62) and for C_{max} was 0.73 (0.68, 0.79), with no observed change in t_{max}. Following co-administration of bosentan with tadalafil, bosentan ratios for AUC_τ and C_{max} were 1.13 (1.02, 1.24) and 1.20 (1.05, 1.36), respectively, and fully contained within bioequivalence range for AUC_τ (0.80-1.25) and C_{max} (0.70-1.43). Once daily doses of 40 mg tadalafil alone and in combination with twice-daily doses of 125 mg bosentan for 10 days were generally well tolerated.

CONCLUSION: After 10 days of co-administration, bosentan decreased tadalafil exposure by 41.5% with no significant difference in bosentan exposure.

CLINICAL IMPLICATIONS: These pharmacokinetic differences are considerably less than those reported with another PDE5 inhibitor, sildenafil in combination with bosentan; whereby no dose adjustment is necessary (USPI, Tracleer®). Therefore, patients may receive concomitant tadalafil and bosentan therapy without dose adjustments.

DISCLOSURE: Rebecca Wrishko, Shareholder Eli Lilly and Company; Employee Eli Lilly and Company.

NO CLINICALLY RELEVANT PHARMACOKINETIC INTERACTION BETWEEN AMBRISANTAN AND SILDENAFIL

Christopher Dufton PhD^{*} Michael J. Gerber MD Ophelia Yin PhD Christine Brandquist PharmD Hossein A. Ghofrani MD Myogen Inc., Westminster, CO

PURPOSE: Ambrisentan is a high affinity, propanoic acid-class, ETA-selective endothelin receptor antagonist (ERA). Ambrisentan doses of 2.5 and 5 mg once-daily have been shown to improve 6-minute walk distance and delay clinical worsening in a placebo-controlled study (ARIES-2) of patients with pulmonary arterial hypertension (PAH), with no incidence of serum aminotransferases >3xULN. Sildenafil is a phosphodiesterase type 5 inhibitor approved for PAH. Co-administration of sulfonamide-class ERAs have been shown to decrease (bosentan) or increase (sitaxsentan) the systemic exposure (AUC) of sildenafil, while sildenafil has been shown to increase the AUC of bosentan. Therefore, the potential for pharmacokinetic (PK) interactions between ambrisentan and sildenafil were examined.

METHODS: A 2-period crossover study was conducted in 19 healthy adults. Ambrisentan exposure (AUC_{0-last}) and maximum plasma concentration (C_{max}) were determined over a 24-hour period for a 10 mg dose of ambrisentan alone and after 7 days of dosing with sildenafil 20 mg tid. The AUC_{0-last} and C_{max} for sildenafil and n-desmethyl-sildenafil (active metabolite) were determined over a 24-hour period for a 20 mg dose of sildenafil alone and after 7 days of dosing with ambrisentan 10 mg qd.

RESULTS: Ambrisentan C_{max} was unchanged (-3.7% [90% CI: -14.0% to +7.8%]) and a minor increase in AUC_{0-last} (+6.0% [90% CI: +0.6% to +11.7%]) was observed after sildenafil administration. Sildenafil C_{max} was increased slightly (+13.4% [90% CI: -0.4% to +29.1%]) and AUC_{0-last} was unchanged (+0.4% [90% CI: -8.8% to +10.5%]) after ambrisentan administration; whereas, C_{max} for n-desmethyl-sildenafil was unchanged (-0.4% [90% CI: -12.8% to +13.8%]) and AUC_{0-last} for n-desmethyl-sildenafil was slightly lower (-7.6% [90% CI: -14.9% to +0.4%]).

CONCLUSION: Multiple doses of ambrisentan had no clinically relevant effect on the pharmacokinetics of sildenafil or n-desmethyl-sildenafil. Similarly, multiple doses of sildenafil had no clinically relevant effect on the pharmacokinetics of ambrisentan.

CLINICAL IMPLICATIONS: Co-administration of ambrisentan and sildenafil should not require dose adjustment of either drug compared to administration alone.

DISCLOSURE: Christopher Dufton, Employee Myogen, Inc.; Product/procedure/technique that is considered research and is NOT yet approved for any purpose, ambrisentan.

CORRELATION OF WHO FUNCTIONAL CLASS AND INDICES OF DISEASE SEVERITY IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION: INSIGHTS FROM EARLY, BREATHE-1 AND 351 STUDIES

Nazzareno Galie MD^{*} Lewis J. Rubin MD Marius M. Hoepfer MD Anđjela Kusic-Pajic MD Eleonora Chiossi MSc Gerald Simonneau MD University of Bologna, Bologna, Italy

PURPOSE: WHO Functional Class (WHO FC) is used as a means of classifying disease severity in pulmonary arterial hypertension (PAH). However, comparisons of objective measures of disease severity among