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In Reply: Telotristat Ethyl for Patients With Carcinoid Syndrome Associated With Chest Pain and Hypertension

To the Editor:

In the January 2018 issue, Dr Kasi recently reported prescribing telotristat ethyl to 3 patients with carcinoid syndrome and observing grade 3 chest pain and hypertension in all of them, each case within 1 month of initiating treatment.¹ Here we review the clinical trial experience and postmarketing surveillance for these adverse events.

The safety and efficacy of telotristat ethyl were established during phase 3, randomized, placebo-controlled, double-blind clinical trials enrolling subjects with carcinoid syndrome not adequately controlled by current somatostatin analog therapy.^{2–4}

During the TELESTAR study, subjects received double-blind placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg 3 times daily for 12 weeks (N = 135).² Subsequently, they entered a 36-week open-label extension phase during which subjects received telotristat ethyl 500 mg 3 times daily (N = 115).³ During the TELECAST study, subjects received double-blind placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg 3 times daily for 12 weeks (N = 76).⁴

In the integrated safety analysis data from the TELESTAR and TELECAST studies, the incidences of chest pain during the 12-week double-blind treatment period among subjects treated with placebo and telotristat ethyl were 0 and 0.7% (n = 1), respectively. The incidences of hypertension among subjects treated with placebo and telotristat ethyl were 1.4% (n = 1) and 2.9% (n = 4), respectively. In addition, 1 placebo patient and no patient on telotristat ethyl experienced increased blood pressure. At the end of the double-blind treatment period, the mean change from baseline in systolic blood pressure among all subjects who initiated telotristat ethyl was +1 mm Hg. Similarly, the mean change in diastolic blood pressure was +1 mm Hg. There were no serious adverse events related to chest pain or hypertension in these phase 3 studies.⁵

Among subjects with preexisting carcinoid heart disease treated with telotristat ethyl, there was no difference between the adverse event profile of this subgroup and the overall study populations.^{4,6}

During the postmarketing experience with telotristat ethyl through December 1, 2017, Lexicon Pharmaceuticals has received a small number of reports for chest pain and hypertension, which is consistent with the clinical trial experience.⁷ Postmarketing safety surveillance efforts are ongoing.

All authors are Lexicon Pharmaceuticals, Inc, employees.

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Metformin and Pancreatic Cancer Risk in Patients With Type 2 Diabetes

To the Editor:

Patients with pancreatic cancer (PC) have very poor prognosis, and the 5-year survival is as low as 6%.^{1,2} Risk factors of PC include diabetes, obesity, smoking, pancreatitis, and family history.³ Although metformin use in diabetes patients is associated with a reduced risk of PC in a meta-analysis,⁴ a recent case-control study conducted in the United States did not confirm such a protective effect.⁵ Because data from Asian populations are still sparse, this study evaluated whether metformin might reduce PC risk in Taiwanese patients with type 2 diabetes mellitus, using the reimbursement database of Taiwan's National Health Insurance.

Detailed methodology has been reported previously.^{6,7} Disease diagnoses were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification*. Diabetes was coded 250.XX and PC was coded 157.

A cohort of 12,616 pairs of metformin ever users and never users matched on propensity score using the Greedy 8 → 1 digit match algorithm was enrolled from new-onset diabetes patients diagnosed during the period from 1999 to 2005, following the steps shown in Figure 1. Patients with a diagnosis of pancreatic disease (*International Classification of Diseases, Ninth Revision, Clinical Modification* 577), alcohol-related diagnoses (291, 303, 535.3, 571.0–571.3, and 980.0), and gallstone (574.00, 574.01, 574.10, 574.11, 574.20, 574.21, and A348) were excluded to avoid their residual confounding.

Propensity score was derived from the date of entry plus covariates including age, sex, occupation, living region, hypertension (401–405), dyslipidemia (272.0–272.4), obesity (278), nephropathy (580–589), eye disease (250.5, 362.0, 369, 366.41, and 365.44), stroke (430–438), ischemic heart disease (410–414), peripheral arterial disease (250.7, 785.4, 443.81, and 440–448), chronic obstructive pulmonary disease (490–496), tobacco abuse (305.1, 649.0, and 989.84), history of *Helicobacter pylori* infection, insulin, sulfonylurea, meglitinide, acarbose, rosiglitazone, pioglitazone, angiotensin converting enzyme inhibitor/angiotensin