NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: A Real-World Study Evaluating the Safety of Pantoprazole Sodium intravenous (IV) in Infants Aged 1 Month to <1 Year and Patients Aged 1 to <2 Years Using an Electronic Health Records Database from the United States

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Rationale and background: Protonix® (pantoprazole sodium) intravenous (IV) for injection is indicated for the treatment of adult patients only with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE). Currently, there is an ongoing clinical trial (B1791089) investigating the use of pantoprazole sodium in patients 1 to 16 years of age. However, use in infants and particularly those under two years is difficult to study. Therefore, this non-interventional study is designated as a Post-Authorization Safety Study (PASS) and was proposed voluntarily to the U.S. FDA by Pfizer to collect safety data.

Research question and objectives: The primary objective was to estimate the incidence rate (IR) of the outcomes of interest listed below in infants aged 1 month to <1 year (Cohort 1) and patients aged 1 to <2 years (Cohort 2) with a diagnosis of GERD with or without EE, treated with IV pantoprazole. The secondary objectives were to estimate the IR of outcomes of interest in infants from Cohort 1 and in patients from Cohort 2 treated with IV pantoprazole without a diagnosis of GERD or EE, and to provide the frequency of the 25 most common diagnostic codes occurring within 30 days prior to or on the starting date of IV pantoprazole through 90 days of last treatment with IV pantoprazole among infants in Cohort 1 and patients in Cohort 2 with a diagnosis of GERD (regardless of EE diagnosis).

Outcomes of interest included:

- Agranulocytosis
- Thrombocytopenia
- Leukopenia
- Pancytopenia
- Hypersensitivity
- Hyperlipidemia
- Hypertriglyceridemia
- Hyponatremia
- Hypomagnesemia
- Hypocalcemia

- Hypokalemia
- Diarrhea
- Vomiting
- Abdominal distension
- Hepatobiliary injury
- Urticaria
- Angioedema
- Stevens-Johnson syndrome
- Lyell syndrome
- Erythema multiforme
- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
- Tubulointerstitial nephritis
- Photosensitivity
- Peripheral edema
- Injection site thrombophlebitis

Study design: A retrospective cohort study was conducted using Optum's Market Clarity US dataset. The study period was defined from 01 January 2007 to 31 December 2020. The index date was defined as the first administration of IV pantoprazole. Patients were included if they had at least one administration of IV pantoprazole during the study period, if they were enrolled for at least 30 days in the database prior to the index date, and if they were 1 month to < 1 year on the index date for Cohort 1 and 1 year to <2 years on the index date for Cohort 2. Patients were excluded if they had International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes occurring prior to or on the index date indicating a preterm birth or birth weight less than 2.36 kilograms. Within each cohort, 3 subgroups were identified using ICD-9-CM or ICD-10-CM codes: Subgroup 1 (GERD With EE), Subgroup 2 (GERD without EE), and Subgroup 3 (no diagnosis of GERD or EE). The outcomes of interest were defined by the presence of at least one ICD-9-CM or ICD-10-CM diagnosis code identified in the inpatient or outpatient setting during the follow-up period. Patients were followed from index date to whichever of the following occurred first: occurrence of the outcome of interest, 90 days following the last date of IV pantoprazole administration, initiation of a separate IV pantoprazole infusion within 90 days following the discontinuation of IV pantoprazole administration, death, end of enrollment in the database, or end of the study period. IRs per 1,000 person-years (PY) and 95% confidence intervals (CI) of outcomes were estimated in each cohort and in all 3 subgroups. Within the overall cohort and in the 3 subgroups, results were stratified by duration of IV pantoprazole treatment (<4 days, ≥ 4 days). Two sensitivity analyses removing the 30-day enrollment restriction and stratifying by ICD-9-CM versus ICD-10-CM subgroup identification were also conducted.

Setting: The study was conducted using Optum's Market Clarity US dataset, which includes data from adjudicated administrative insurance claims, and inpatient and outpatient electronic health records (EHR). The population of the dataset is made up of commercial health plan members and Medicare Advantage members across all 50 states. The database

currently encompasses the claims and EHR data of approximately 1.9 million patients aged less than 2 years from 01 January 2007 through 31 December 2020.

Subjects and study size, including dropouts: Cohort 1 (N=1,879) and Cohort 2 (N=981) included patients who had at least one administration of IV pantoprazole during the study period after meeting all inclusion and exclusion criteria. No patients were identified in Subgroup 1 in either of the cohorts. In Cohort 1, 851 (45.3%) and 1,028 (54.7%) patients were identified in Subgroups 2 and 3, respectively. In Cohort 2, 462 (47.1%) and 519 (52.9%) patients were identified in Subgroups 2 and 3, respectively.

Variables and data sources: The Optum Market Clarity dataset contains electronic health records data with prescriptions, diagnoses, and provider information as well as practice management data and claims information for deterministically-matched patients. Exposure to IV pantoprazole was identified from inpatient procedure and drug codes including National Drug Code (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes. Only the first pantoprazole treatment episode during the study period was of interest, where an episode was defined by a gap of <7 days between administrations. The outcomes of interest were as described under the objectives. Key variables of interest included demographic characteristics such as age on the index date, race/ethnicity, gastrointestinal comorbidities and treatment for esophageal, gastric, pyloric channel, or duodenal ulceration, and duration and dose of IV pantoprazole.

Results:
Cohort 1 (Infants aged 1 month to <1 year): The reported incidence rates of the outcomes of interest ranged from 0.0 to 742.8 per 1,000 PY in Cohort 1, with the highest IRs of vomiting [742.80 per 1,000 PY, 95% CI: (638.54, 847.05)], diarrhea [377.77 per 1,000 PY, 95% CI: (312.58, 442.96)], abdominal distension (214.31 per 1,000 PY, 95% CI: (165.81, 262.81)], hyponatremia [204.99 per 1,000 PY, 95% CI: (157.96, 252.01)], and hypokalemia [203.49 per 1,000 PY, 95% CI: (156.49, 250.49)]. No patients were identified in Subgroup 1 in this cohort and the IRs remained comparable in Subgroup 2 and Subgroup 3. When stratified by duration of pantoprazole IV treatment, most IRs were numerically higher among the infants treated with IV pantoprazole for ≥4 days compared to those treated with IV pantoprazole for <4 days, specifically for the outcomes of hypokalemia, hyponatremia, hepatobiliary injury, and thrombocytopenia. When sensitivity analyses removing the 30-day enrollment restriction and stratifying by ICD coding schema were conducted, IRs of the outcomes remained comparable with the main analysis. The most commonly occurring outcomes with the highest IRs were vomiting, diarrhea, and abdominal distension in this cohort and both subgroups within this cohort and this is consistent with the known safety profile of pantoprazole.

Cohort 2 (Patients aged 1 year to <2 years): The reported incidence rates of the outcomes of interest ranged from 0.0 to 711.82 per 1,000 PY in Cohort 2, with the highest IRs of vomiting [711.82 per 1,000 PY, 95% CI: (550.73, 872.92)], diarrhea [412.36 per 1,000 PY, 95% CI: (308.02, 516.70)], abdominal distension [234.93 per 1,000 PY, 95% CI: (163.88, 305.97)], hypokalemia [195.37 per 1,000 PY, 95% CI: (131.55, 259.19)] and hyponatremia [182.53 per 1,000 PY, 95% CI: (121.17, 243.88)]. No patients were identified in Subgroup 1 in this cohort and the IRs remained comparable in Subgroup 2 and Subgroup 3. When stratified by

duration of pantoprazole IV treatment, IRs were numerically higher for many outcomes among patients treated with IV pantoprazole for ≥4 days compared to <4 days, specifically for hypokalemia and abdominal distension. When sensitivity analyses removing the 30-day enrollment restriction and stratifying by ICD coding schema were conducted, IRs of the outcomes remained comparable with the main analysis. As described in Section 11.3, the most commonly occurring outcomes with the highest IRs were vomiting, diarrhea, and abdominal distension in this cohort and in both subgroups within the cohort and this is consistent with the known safety profile of pantoprazole.

Discussion: This retrospective cohort study estimated incidence rates of safety outcomes of interest in two separate cohorts of infants aged 1 month to <1 year and patients aged 1 year to <2 years treated with IV pantoprazole in the real-world setting using the Optum Market Clarity database from the US during the study period of 01 January 2007 and 31 December 2020. No patients with a diagnosis of GERD with EE (Subgroup 1) were identified in either of the cohorts of interest and over 50% of the patients in both cohorts were identified as patients without a diagnosis of GERD or EE. The key variables of interest such as demographic characteristics and GI comorbidities were comparable in Subgroups 2 and 3 in both cohorts. Consistent with the known safety profile of pantoprazole, the most commonly occurring outcomes with the highest IRs were vomiting, diarrhea, and abdominal distension in both cohorts and within both subgroups in each cohort. When stratified by duration of pantoprazole IV treatment, most IRs were numerically higher among the infants treated with IV pantoprazole for ≥4 days compared to those treated with IV pantoprazole for <4 days, specifically for the outcomes of hypokalemia, hyponatremia, hepatobiliary injury, and thrombocytopenia in Cohort 1 and specifically for hypokalemia and abdominal distension in Cohort 2.

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