**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | PPI and $H_2$RAs |
| Study Code | D9612N00016 |
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# Drug utilization and safety outcomes among children using esomeprazole, other proton pump inhibitors or histmain-2 receptor antagonists

**Study dates:** Observational, cohort study with prospective data collection covering the period September 2008 and August 2011

**Phase of development:** Therapeutic use

**Principal Investigator:**

**Sponsor's Responsible Medical Officer:**

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## Study centre(s)

NL

## Objectives

- to provide a detailed description of demographic factors, drug use, medical history and treatment characteristics among children (age 0-18 years) that are prescribed esomeprazole, other PPIs and H2RAs for the first time.
- to evaluate the safety of esomeprazole, other PPIs and H2RAs in children by reporting all incident hospitalized cases of angioneurotic oedema, pneumonia, gastroenteritis, failure to thrive, convulsion/seizures, acute interstitial nephritis and thrombocytopenia.

## Study design

An observational, cohort study with prospective data collection using data from PHARMO Database Network in the Netherlands.

## Methods

All children aged 0-18 years in the PHARMO network who received a dispensing of esomeprazole, other PPIs (omeprazole pantoprazole, lansoprazole, rabeprazole) or H2RAs (cimetidine, ranitidine, famotidine, nizatidine) between September 1st 2008 and August 31st 2011 were included in the source population. The study started the month Nexium Sachet became available on the Dutch market. Subjects were identified during a 3 year period with a follow-up period of 18 months after the last included patients and were followed up to December 31st 2013.

Children were included in one of three cohorts according to their index treatment (first treatment within study period): esomeprazole cohort (index cohort), other PPI cohort (reference cohort A) and H2RA cohort (reference cohort B). Date of first dispensing was called the cohort entry date (CED). Children with less than one year of history in PHARMO before CED were excluded. If a child was <1 year at CED history from birth was required. Children who did not receive any other acid-suppressing drug at any time before CED were categorized as naïve children. Children who received non-index acid suppression drugs more than a year prior to CED were categorized as non-naïve.

The following safety events were identified using the primary discharge diagnosis codes to define safety events during the available follow-up up to 18 months after CED: angioneurotic edema, pneumonia, gastroenteritis, failure to thrive, convulsion/seizure, acute interstitial nephritis and thrombocytopenia.

Discharge diagnoses for safety events were validated by review of discharge letters. Validation was possible for 27% of the safety events. Overall, 40-69% of safety events were confirmed without doubt and for 20-50% of events, categorized as probably or not confirmed, most often due to insufficient information in the discharge letter. Overall, 3-17% of cases were classified as “no case”.

## Statistical analysis

Differences in categorical patient and treatment characteristics were assessed by comparing esomeprazole users with reference A users (other PPI cohort) and esomeprazole users with reference B users (H2RA cohort) using logistic regression analyses. Differences in numerical patient and treatment characteristics were assessed by linear regression methods. The odds ratios (OR) and estimates were adjusted for age and gender and are presented with their 95% confidence intervals (CI). Differences in prescribed doses were not assessed, as the age-dependent recommended doses of PPIs and H2RA are substantially different for the drugs included in this study and are also dependent on age.

## Summary of results

The study population consisted of 23,470 patients who were using a single PPI or H2RA aged 0-18 years, with at least one year history available or eligible from birth, who had not used the same drug in the year before. Of these, 2,820 (12%) children were included in the esomeprazole group, 13,818 (59%) in the other PPI group, and 6,832 (29%) in the H2RA group. The majority of the esomeprazole (67%) and H2RA (63%) users were <12 years of age while the majority of other PPI users were ≥12 years (69%). Furthermore, 45% of esomeprazole and H2RA users and 16% of other PPI users started therapy in the first year of life.

Most children (71-88%) had only one treatment episode during follow-up with a mean duration (± SD) of 2.9 (±4.9) months in esomeprazole users, 1.8 (±3.0) months in other PPI users, and 3.4 (±3.9) months in H2RA users. Mean duration of all treatment episodes was 5.0 (±8.1) months in esomeprazole users, 2.9 (±5.2) months in other PPI users and 3.9 (±4.6) months in H2RA users.

Having a history of epilepsy and asthma/COPD was more common in children being dispensed esomeprazole as compared to those treated with other PPIs or H2RAs (Table 1). More children included in the esomeprazole group received the first prescription from a specialist (68%), while this was observed in 23% in the H2RA group and 31% in the other PPI group.

Hospital admissions for safety outcomes were infrequent, overall 2% were hospitalized for any pre-specified outcomes in the period of up to 18 months follow-up. Comparative analyses between cohorts with regard to these safety events were planned but the numbers of safety events were limited and it was not meaningful to conduct formal statistical analyses (Table 2). Most frequent hospitalizations were gastroenteritis (1%), convulsion/seizure (1%) and failure to thrive (<0.5%).

## Table 1: General co-morbidity in the entire available history

| | **Esomeprazole** | **Reference A Other PPI** | **Reference B H2RA** | **Esomeprazole vs. Reference A Other PPI** | **Esomeprazole vs. Reference B H2RA** |
|---|---|---|---|---|---|
| | **N=2,820** | **N=13,818** | **N=6,832** | | |
| | **n (%)** | **n (%)** | **n (%)** | **OR (95%CI)*** | **OR (95%CI)*** |
| Esophageal diseases | 165 (6) | 247 (2) | 148 (2) | 1.67 (1.35 - 2.06) | 2.72 (2.16 - 3.41) |
| Esophagitis | 157 (6) | 243 (2) | 146 (2) | 1.57 (1.27 - 1.95) | 2.61 (2.07 - 3.28) |
| Heartburn | 0 (-) | 1 (<0.5) | 2 (<0.5) | - | - |
| Congenital anomalies of upper alimentary tract | 13 (<0.5) | 28 (<0.5) | 33 (<0.5) | 1.22 (0.62 - 2.40) | 0.90 (0.47 - 1.72) |
| **Gastrointestinal diseases** | | | | | |
| IBS | 3 (<0.5) | 20 (<0.5) | 2 (<0.5) | 1.34 (0.39 - 4.58) | 4.15 (0.69 - |
| Peptic ulcer | 1 (<0.5) | 0 (-) | 0 (-) | - | - |
| **Neurological** | | | | | |
| Epilepsy | 89 (3) | 213 (2) | 64 (1) | 2.36 (1.82 - 3.07) | 3.52 (2.54 - 4.87) |
| Quadriplegia | 1 (<0.5) | 2 (<0.5) | 0 (-) | 4.41 (0.40 - | - |
| Cerebral palsy | 12 (<0.5) | 25 (<0.5) | 6 (<0.5) | 2.64 (1.29 - 5.40) | 4.99 (1.87 - |
| Hydrocephalus | 4 (<0.5) | 7 (<0.5) | 4 (<0.5) | 1.90 (0.53 - 6.89) | 2.37 (0.59 - 9.51) |
| Anemia | 8 (<0.5) | 16 (<0.5) | 2 (<0.5) | 3.27 (1.34 - 8.01) | 10.09 (2.14 - |
| Asthma/COPD | 253 (9) | 1,030 (7) | 368 (5) | 1.39 (1.20 - 1.62) | 1.78 (1.50 - 2.10) |
| Diabetes | 10 (<0.5) | 84 (1) | 13 (<0.5) | 0.97 (0.50 - 1.90) | 2.02 (0.88 - 4.62) |
| Cardiovascular disease | 37 (1) | 64 (<0.5) | 45 (1) | 1.65 (1.08 - 2.52) | 1.96 (1.26 - 3.03) |

PPI: proton pump inhibitors; H2RA: histamine-2-receptor antagonist; OR: odds ratio; CI: confidence interval; *Adjusted for age and gender; IBS: irritable bowel syndrome; COPD: chronic obstructive pulmonary disease; For all OR the reference group included patients that did not suffer from the co-morbidity in the entire available history.

*Note: General co-morbidity was based on hospitalizations in the entire available history and/or drug dispensings in the year before cohort entry date for epilepsy, asthma/COPD and diabetes; all other co-morbidities were based on hospitalizations only.*

Table 2: Number of safety events based on hospitalizations up to 18 months follow-up

| | **Esomeprazole** | **Reference A Other PPI** | **Reference B H2RA** | **Total** |
|---|---|---|---|---|
| | **N=2,820** | **N=13,818** | **N=6,832** | **N=23,470** |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Angioneurotic edema | 0 (-) | 1 (<0.1) | 0 (-) | 1 (<0.1) |
| Pneumonia | 38 (1) | 48 (<0.5) | 38 (1) | 124 (1) |
| Gastroenteritis | 54 (2) | 83 (1) | 87 (1) | 224 (1) |
| Failure to thrive | 13 (<0.5) | 19 (<0.5) | 16 (<0.5) | 48 (<0.5) |
| Convulsion/seizure | 28 (1) | 53 (<0.5) | 42 (1) | 123 (1) |
| Acute interstitial nephritis | 1 (<0.1) | 2 (<0.1) | 0 (-) | 3 (<0.1) |
| Thrombocytopenia | 2 (<0.1) | 8 (<0.1) | 2 (<0.1) | 12 (<0.1) |

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