RANITIDINE AND OTHER HISTAMINE-H_2-RECEPTOR ANTAGONISTS – A DRUG UTILISATION STUDY

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PASS information

Title	Ranitidine and other histamine H_2-receptor antagonists – a drug utilisation study
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Active Ingredient	Ranitidine Cimetidine Famotidine Nizatidine Niperotidine Roxatidine Ranitidine bismuth citrate Lafutidine
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Research question and objectives	Ranitidine is a competitive and reversible inhibitor of the action of histamine and indicated for the management of peptic ulceration, Gastro-Esophageal Reflux Disease (GERD), reflux oesophagitis and Zollinger-Ellison syndrome. Results of a preliminary laboratory analysis have shown the presence of N-Nitrosodimethylamine (NDMA), a human carcinogen, in ranitidine. With this DUS, we aim to determine drug utilisation and prescription patterns of medicinal products containing H_2-receptor antagonists. These data will give insight on the number of patients using ranitidine and thus potentially at risk of NDMA. In particular we will: 1. Study the prevalence and incidence prescribing of H_2-receptor antagonists as a class and by individual drug

	2. Explore the characteristics of H_2-receptor antagonist use with regard to age (10-years age categories), sex, formulation, daily dose, duration and cumulative exposure by class level and individual ingredient 3. Explore the indication of use of H_2-receptor antagonist by class level, individual ingredient and by formulation 4. Explore the proportion of patients treated with H_2-receptor antagonists suffering from chronic renal impairment by class level and by individual ingredient.
Country(-ies) of study	Belgium, France, Germany, The Netherlands, UK
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Marketing authorisation holder(s)

Marketing authorisation holder(s)	Not applicable
MAH contact person	Not applicable

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1 List of abbreviations

Abbreviation	Name
ATC	Anatomical Therapeutic Chemical Classification
CDM	Common Data Model
CHMP	Committee for Medicinal Products for Human Use
DDD	Defined Daily Dose
DUS	Drug Utilisation Study
EHR	Electronic Healthcare Record
ETL	Extract Transform Load
GERD	Gastro-oesophageal reflux disease
H_2	Histamine 2
IQR	Interquartile range
NAP	Not applicable
NDMA	N-Nitrosodimethylamine
OTC	Over The Counter
PDD	Prescribed Daily Dose
Q1	First Quartile
Q3	Third Quartile

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3 Abstract

Title

Ranitidine and other histamine-H_2-receptor antagonists – a drug utilisation study

Version and Date: 17th January 2020 - Protocol Version 1.0
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Rationale and background:

Ranitidine is a competitive and reversible inhibitor of the action of histamine and indicated for the management of peptic ulceration, Gastro-Esophageal Reflux Disease (GERD), reflux oesophagitis and Zollinger-Ellison syndrome.

Results of a preliminary laboratory analysis have shown the presence of N-Nitrosodimethylamine (NDMA), a human carcinogen, in ranitidine. At the request of the European Commission, the EMA's Committee for Medicinal Products for Human Use (CHMP) is evaluating all available data to assess whether patients using ranitidine are at any risk from NDMA and whether regulatory action is warranted at EU level to protect patients and public health.

Data about prescribing and use patterns of ranitidine-containing medicines in EU Member States will inform on the population at risk of exposure to NDMA (or other nitrosamines) through use of ranitidine. It will also provide information on usage patterns for different substances of the class informing on usage of substances alternative to ranitidine.

With this DUS, we aim to determine drug utilisation and prescription patterns of medicinal products containing H_2-receptor antagonists.

Research question and objectives

With this study we aim to: i) study the prevalence and incidence of exposure to H_2-receptor antagonists as a class and by individual ingredient, ii) explore the characteristics of H_2-receptor antagonist use in terms of observation time, cumulative duration, cumulative dose and cumulative annual dose for the class as a whole and by individual ingredient with regard to age, sex, formulation, daily dose iii) explore the indication of use of H_2-receptor antagonist by class level, individual ingredient and by formulation, iv) explore the proportion of patients treated with H_2-receptor antagonists suffering from renal impairment.

Study design

Retrospective Cohort Study using electronic health care records from six databases from six European countries: Belgium (LPD Belgium), the Netherlands (IPCI), Germany (DA Germany), France (DA France), UK (IMRD) and Spain (SIDIAP).

Population

The study population will consist of all available data in the databases (1992-2019).

Variables

From the drug exposure records, drug use defined as the number of users of H_2-receptor antagonists will be calculated. This will be investigated both for prevalent and incident use of H_2-receptor antagonist.

Dosing will be described by the median PDD (Prescribed Daily Dose)/DDD (Defined Daily Dose) ratio and by the number of patients within the different strata of PDD/DDD ratio. The Cumulative exposure will be expressed by the cumulative duration, by the cumulative dose (in mg and DDD) and cumulative annual dose (mg/PY).

The indication of use for the H_2-receptor antagonists as well as chronic renal impairment as underlying comorbidity will be investigated.

Data will be presented for all indications, and also for particular indications (i.e. GERD, Zollinger Ellison syndrome, gastric ulcer, duodenal ulcer), by H_2-receptor antagonist class level, by individual H_2-receptor antagonist ingredient and by formulation (oral (solid or liquids) or parenteral). Study data will also be presented by database as well as by age categories (0-<18 years; 18-<75 years; >=75years), sex, and calendar year, and in some cases by cumulative drug exposure duration strata according to the ICH M7 strata (≤1 month; >1-12 months; >1-10 years; > 10 years).

Data sources

For this study, we will include Electronic Healthcare Record data from six primary care databases throughout Europe: IPCI (the Netherlands), SIDIAP (Spain), IMRD (UK), LPD (Belgium), DA Germany and DA France. All these databases have their data mapped to the OMOP Common Data Model.

Study size

As no hypothesis will be tested for this study, no sample size calculation has been conducted.

Data analysis

As this is a DUS study without a priori hypothesis, descriptive statistical analysis will be used.

Milestones

Milestone	**Planned date**
Approval Study Protocol by EMA	17th January 2020
<Registration in the EU PAS register>	*Date*
Start of data collection	Not applicable – EHR databases will be used where all data has already been collected
End of data collection	Not applicable – EHR databases will be used where all data has already been collected
Draft report	13th March 2020
Final study report accepted by EMA	27th March 2020
Manuscript to be provided to EMA	29th May 2020

4 Amendments and updates

There have been no formal amendments to the protocol so far.

Number	Date	Section of study protocol	Amendment or update	Reason
1				
2				
…				

5 Milestones

Milestone	**Planned date**
Approval Study Protocol by EMA	17th January 2020
<Registration in the EU PAS register>	*Date*
Start of data collection	Not applicable – EHR databases will be used where all data has already been collected
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Draft report	13th March 2020
Final study report accepted by EMA	27th March 2020
Manuscript to be provided to EMA	29th May 2020

6 Rationale and background

Ranitidine is a competitive and reversible inhibitor of the action of histamine, released by enterochromaffin-like (ECL) cells, at the histamine H_2-receptors on parietal cells in the stomach. It is indicated for the management of peptic ulceration, Gastro-Oesophageal Reflux Disease (GERD), reflux oesophagitis, Zollinger-Ellison syndrome, chronic episodic dyspepsia, peptic ulcer haemorrhage, prophylaxis of stress ulceration, Mendelson's syndrome, duodenal ulcers, benign gastric ulcers, post-operative ulcer, symptomatic relief of heart burn, dyspepsia (acid indigestion), hyperacidity, and prevention of symptoms associated with consuming food and drink. Ranitidine is available for oral and parenteral administration. (Ching and Lam 1995; 2012)

Results of a preliminary laboratory analysis have shown the presence of N-Nitrosodimethylamine (NDMA), a human carcinogen, in ranitidine, a H_2-receptor antagonist. (Mahase 2019) The results on a limited sample of products showed that NDMA was above the acceptable intake for the majority of ranitidine active pharmaceutical ingredient and finished products.

At the request of the European Commission, the EMA's Committee for Medicinal Products for Human Use (CHMP) is evaluating all available data to assess whether patients using ranitidine are at any risk from NDMA and whether regulatory action is warranted at EU level to protect patients and public health. Data about prescribing and use patterns of ranitidine-containing medicines in EU Member States will inform on the population at risk of exposure to NDMA (or other nitrosamines) through use of ranitidine. It will also provide information on usage patterns for different substances of the class informing on usage of substances alternative to ranitidine

To answer these questions, the EMA launched an invitation to tender under Lot 3 – Rapid Descriptive Studies. As part of this tender, we will conduct a DUS with as aim to determine drug utilisation and prescription patterns of medicinal products containing H_2-receptor antagonists.

In particular we will investigate the frequency of use, the cumulative exposure (with regard to cumulative duration, cumulative dose expressed in mg, number of DDDs and cumulated annual dose) as well as the median daily exposure (expressed as PDD/DDD ratio). In addition, the indication of use of H_2-receptor antagonists will be explored and, as NDMA toxicity might be aggravated in patients with chronic renal failure, the presence of chronic renal impairment during exposure to H_2-receptor antagonists will be investigated.

7 Research question and objectives

With this study, we want to explore the real-world use of ranitidine and other H_2 antagonists and in particular will:

- Study the prevalence and incidence of exposure to H_2-receptor antagonists for the class as a whole and by individual ingredient.
- Explore the characteristics of H_2-receptor antagonist use with regard to age (10-years age categories), sex, formulation, daily dose, observation time, cumulative duration, cumulative dose (in mg and DDD) and cumulative annual dose for the class as a whole and by individual ingredient.
- Explore the indication of use of H_2-receptor antagonists for the class as a whole, by individual ingredient and by formulation.
- Explore the proportion of patients treated with H_2-receptor antagonists suffering from chronic renal impairment by class level and by individual ingredient.

8 Research methods

8.1 Study design

We will conduct a retrospective cohort study using electronic health care records from six databases from six European countries: Belgium (LPD Belgium), the Netherlands (IPCI), Germany (DA Germany), France (DA France), UK (IMRD) and Spain (SIDIAP).

8.2 Setting

We will use data from six databases from six European countries namely IPCI (the Netherlands), SIDIAP (Catalonia Spain) and IQVIA (UK IMRD, LPD Belgium, DA Germany and DA France). Data of these databases have been mapped to the OMOP Common Data Model (see https://github.com/OHDSI/CommonDataModel/wiki for more details).

For more detailed information on the individual databases, see Section 9.4 'Data sources'.

8.2.1 Study population

The study population consists of all patients with observation time during the study period.

8.2.2 Study period

The study period will start at the first available date in the databases (1992) until the last data cut-off (2019).

8.2.3 Inclusion and exclusion criteria

As described in "Study population", patients will be included in the study if they contribute active follow-up time during the study period. No other inclusion or exclusion criteria will be applied for this study.

8.2.4 Follow-up

For each patient, follow-up will start from the date on which they contribute active follow-up time (= start of observation period) and follow-up will end at the end of the observation period.

8.3 Variables

8.3.1 Drug Exposure

From the study population, we will identify patients exposed to any of the drugs of interest (H_2-receptor antagonists). Drug exposure in the CDM is standardised to RxNorm concepts. This has as advantage that the drug exposure contains details of ingredients, strength, and formulation (Clinical Drug Level), which is not directly available from the ATC code. Cohorts will be constructed for patients exposed to each individual ingredient as well as to the H_2-receptor antagonist drug class.

8.3.2 Prevalent and incident use of H_2-receptor antagonists

Drug use will be assessed per H_2-receptor antagonist ingredient and for the class as whole presented as prevalent and incident drug use. For prevalent drug use, the nominator consists of all patients with at least one day of exposure to the drug of interest in the calendar year. The denominator consists of all patients contributing at least one day of observation time in that calendar year.

For the incidence drug use calculation, the nominator consists of the number of incident users in the year. An incident user is defined as a patient with a record of exposure of interest and no exposure within the previous 365 days. The denominator again consists of all patients contributing at least one day of observation time in that calendar year. This implies that an individual can be defined as an incident user on multiple occasions during the study period. Also, if a person switches between H_2-

receptor antagonists, they may show up as new user of a certain ingredient but be a prevalent user of the class.

8.3.3 Duration of use of H_2-receptor antagonists

For each patient, from all drug exposures, the cumulative duration of use – which is the sum of the duration of treatment episodes - will be calculated. The steps to calculate the cumulative duration of use are described below.

8.3.3.1 Drug Exposure Duration

The duration of each drug exposure will be obtained from the DRUG_EXPOSURE table in the CDM.

The DRUG_EXPOSURE table in the CDM contains the drug_exposure_start_date and the drug_exposure_end_date which are populated based on the available source data during the Extraction Transform and Load (ETL) to the CDM. This has as advantage that the drug exposure duration does not have to be inferred from other information at analysis time. It enables a consistent analytical pipeline for all the databases.

The DRUG_EXPOSURE table contains the following relevant fields for this study:

Field	Description
drug_exposure_start_date	The date of the prescription or dispensing
drug_exposure_end_date	The end date for the current instance of drug exposure. Unless provided directly by the source, this is inferred by the ETL, using other information or a default.
verbatim_end_date	The known end date of a drug exposure as provided by the source.
quantity	The total quantity of drug as recorded in the original prescription or dispensing record.from the physician
days_supply	The number of days of supply of the medication as prescribed. This is defined by the providing physician.
sig	The directions ('signetur') on the drug prescription as recorded in the original prescription (and printed on the container) or dispensing record from the physician.

8.3.3.2 Cumulative exposure duration

Next, from the individual drug exposures, the cumulative exposure duration will be calculated which is the sum of the duration of the individual drug exposures of an individual NOT taking into account gaps between exposures.

An example of the calculation of the cumulative duration is described in figure 1. Figure 1 describes the use of H_2-receptor antagonists in 2 individual patients. Patient A received 3 prescriptions for ranitidine resulting in a cumulative exposure duration of 150 days. As this patient only used ranitidine, the cumulative exposure duration of H_2-receptor antagonists as a class also equals 150 days. In contrast, patient B, received 2 prescriptions of Ranitidine and one of cimetidine. In this scenario, the cumulative exposure duration of H_2-receptor antagonists as a class is different from the cumulative exposure duration of the individual ingredients. In the examples, it is clear that gaps are not taken into account for the calculation of the cumulative exposure duration.

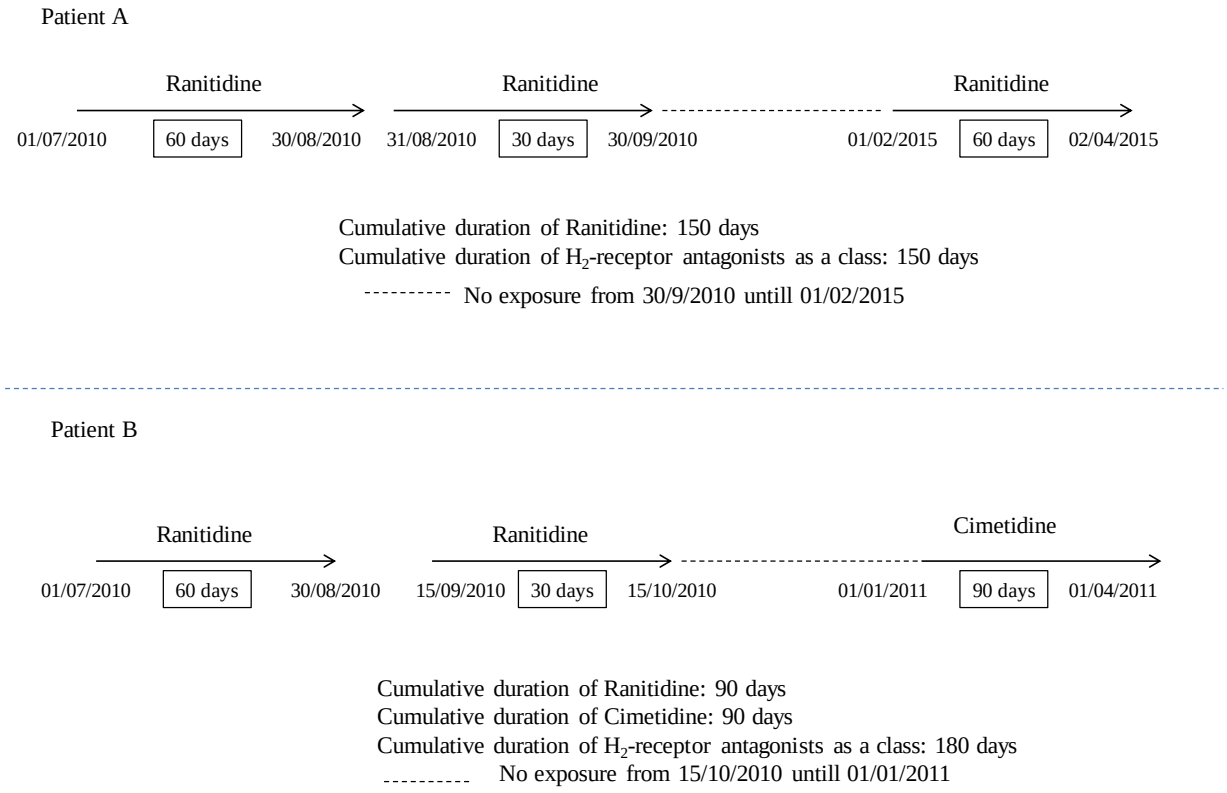


Figure 1: Calculation of cumulative duration

8.3.4 Dose of H_2-receptor antagonists

For each patient, from all drug exposures, the cumulative exposure dose will be calculated.

To compare dosing between the different types of H_2-receptor antagonists, dosing will be expressed by the Prescribed Daily Dosage divided by the Defined Daily Dose (PDD/DDD Ratio). (Grimmsmann and Himmel 2011). The PDD is the daily amount of a drug that is actually prescribed whereas the DDD is the maintenance dose per day for a drug product when used for its major indication in everyday practice. (WHO 2012)

The list with DDD of the different types of H_2-receptor antagonist ingredients is provided in Annex 5.

8.3.4.1 Calculation of PDD

First the PDD needs to be calculated for each Drug Exposure. Similarly, to the duration, there are different ways how the prescribed daily dose (PDD) can be derived from records in the DRUG_EXPOSURE table and the dose information of the DRUG_STRENGTH table (Annex 3), depending on available data:

1) If the **quantity is available**, the calculation of the PDD for solid and liquid formulations is as following:

$$PDD_{solid} = \frac{quantity \times amount\_value\ [amount\_unit\_concept\_id]}{duration}$$

$$PDD_{liquid} = \frac{quantity \times numerator\_value\ [numerator\_unit\_concept\_id]}{duration}$$

2) If the **quantity is not available**, the number of units per day for solid formulations or the volume for liquid formulations needs to be extracted from the sig. The calculation of the PDD for solid and liquid formulations is then as following:

$$PDD_{solid} = number\ of\ units\ per\ day \times amount\_value\ [amount\_unit\_concept\_id]$$

$$PDD_{liquid} = volume\ per\ day \times \frac{numerator\_value}{denominator\_value}\ [numerator\_unit\_concept\_id]$$

We will report the availability of the data elements (quantity, etc.) for each of the drugs of interest in the data sources.

8.3.4.2 Calculation of cumulative (annual) dose

Next the cumulative dose will be calculated and will be expressed in three ways namely i) as the sum of the daily dose in mg, ii) as the sum of the number of DDDs over all drug exposures per type of H_2-receptor antagonist (Brozek, Reichardt et al. 2019; Coupland, Hill et al. 2019) and iii) by the cumulative annual dose.

The cumulative dose will only be provided by ingredient level and not by treatment class as this is not informative.

8.3.4.2.1 Cumulative dose in mg

The formula to calculate the cumulative dose in mg for solid and liquid formulations is as following:

1) If **quantity is available**, the formula to calculate the cumulative exposure in mg is described below:

$$Cumulative\ dose_{solid}[mg] = \sum_{all\ exposures} quantity \times amount\_value\ [mg]$$

$$Cumulative\ dose_{liquid}[mg] = \sum_{all\ exposures} quantity \times numerator\_value\ [mg]$$

2) If the **quantity is missing**, the number of units per day for solid formulations or the volume for liquid formulation needs to be extracted from the sig. The cumulative exposure in mg can then be calculated using the following formula:

$$Cumulative\ dose_{solid}[mg] = \sum_{exposures} units\ per\ day \times amount\_value\ [mg] \times duration$$

$$\text{Cumulative dose}_{\text{liquid}}[\text{mg}] =$$

$$\sum_{exposures} \frac{volume\ per\ day\ \times\ numerator\_value}{denominator\_value}\ [mg] \times\ duration$$

8.3.4.2.2 Cumulative number of DDDs

The formula to calculate the cumulative number of DDDs is described below:

1) If **quantity is available**, the formula to calculate the number of DDDs is described below:

$$Number\ of\ DDD_{solid} = \sum_{exposures} \frac{quantity\ \times\ amount\_value\ [\ amount\_unit\_concept\_id]}{DDD}$$

$$Number\ of\ DDD_{liquid} = \sum_{exposures} \frac{quantity\ \times\ numerator\_value\ [\ numerator\_unit\_concept\_id]}{DDD}$$

2) If the **quantity is missing**, the number of units per day for solid formulations or the volume for liquid formulation needs to be extracted from the sig. The number of DDDs can then be calculated using the following formula:

$$Number\ of\ DDD_{solid} = \sum_{exposures} \frac{units\ per\ day\ \times\ amount_{value}[\ amoun\_unit\_concept\_id] \times\ duration}{DDD}$$

$$Number\ of\ DDD_{liquid} = \sum_{exposures} \frac{\frac{volume\ per\ day\ \times numerator\ value}{denominator\ value}\ [\ numerator\_unit\_concept\_id]\ x\ duration}{DDD}$$

8.3.4.2.3 Cumulative annual dose

The formula to calculate the cumulative annual dose is described below:

$$Cumulative\ annual\ dose = \frac{cumulative\ dose\ in\ mg}{observation\ time\ in\ person\ years}$$

The observation time will start from the date on which patients contribute active follow-up time until the end of the observation period.

We will report the availability of the data elements for each of the drugs of interest in the data sources.

Figure 2 describes the calculation of the cumulative exposure dose.

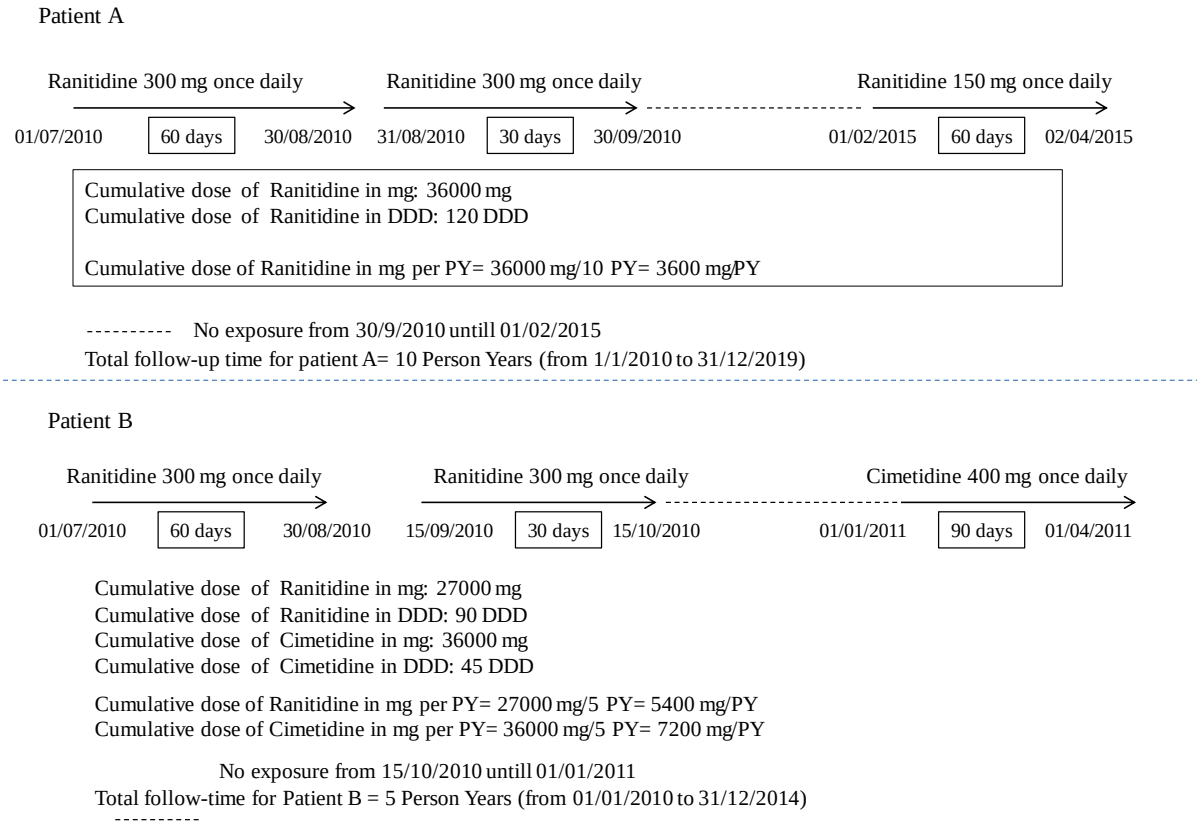


Figure 2: Calculation of cumulative dose

Figure 2 describes the use of H2 receptor antagonists in 2 individual patients. Patient A received 3 prescriptions for ranitidine. The total cumulative exposure dose is 36,000 mg resulting in a cumulative number of DDDs of 120. The cumulative annual dose of ranitidine for this patient is 3,600 mg per year as this patient has 10 years of follow-up.

In contrast, patient B, received 2 prescriptions of Ranitidine and one of cimetidine. In this scenario, the cumulative exposure dose of ranitidine is 27,000 mg with cumulative number of DDDs of 90. The cumulative exposure dose of cimetidine is 36,000 mg with a cumulative exposure dose of 45 DDDs (as patient received 400 mg once daily whereas the DDD of cimetidine is 800 mg – PDD/DDD ratio of 0.5). The cumulative annual dose of ranitidine for this patient is 5,400 mg per year as this patient has 5 years of follow-up and the cumulative annual dose of cimetidine is 7,200 mg per year.

8.3.5 Covariates

Data will be presented by cumulative drug exposure duration strata (≤1 month; >1-12 months; >1-10 years; > 10 years). Age will be assessed at the start of each calendar year. For pediatric use, additional age cut-offs will be used namely the ICH pediatric age categories (small children (<2 years); children (2 to 11 years); adolescents (12 to 18 years). Also, to provide insight in the use of H_2-receptor antagonists in the elderly, apart from the 10-year age categories, age will in addition be categorized into < 18 years, 18-<75 years and >= 75 years.

In addition, we will explore the indication of use of H_2-receptor antagonists and presence of renal impairment in patients exposed to ranitidine

8.3.5.1 Indication of use of H_2-receptor antagonists

The indication of use of H_2-receptor antagonist (for class as a whole, by individual ingredient and by type of formulation (oral or parenteral) will be investigated by checking the presence of conditions prior to the first prescription of H_2-receptor antagonists. The indication of use will be investigated in the past 6 months (180 days) and in the past 12 months (365 days) of the first prescription of the H_2-receptor antagonist during follow-up.

The indication of use will either be GERD, gastric or duodenal ulcer (with or without H Pylori), Zollinger Ellison Syndrome or unknown. The concept sets used for these conditions are available in Annex 4.

8.3.5.2 Presence of chronic renal impairment in patients using H_2-receptor antagonists

The presence of chronic renal impairment in patients using H_2-receptor antagonists will be investigated for the presence of Condition concepts in the 365 days prior to the first H_2-receptor antagonist prescription. The concept sets used for these conditions are available in Annex 4.

8.4 Data sources

For this study, we will include Electronic Health Record data from six primary care databases throughout Europe, in particular IPCI (the Netherlands), SIDIAP (Spain), IMRD (UK), LPD (Belgium), DA Germany and DA France. All of these databases have their data mapped to the OMOP Common Data Model.

Characteristics of these databases with regard to the total number of individuals and database update are described in the table below:

Table 1: Characteristics of databases

Database	Managing Organisation	Country	Individuals	Start Year	Date of last database update
LPD Belgium	IQVIA	Belgium	2.3M	2010	01/2019
DA France	IQVIA	France	7.2M	2009	03/2019
DA Germany	IQVIA	Germany	37.6M	1992	12/2018
UK IMRD	IQVIA	UK	15.2M	1996	09/2018
IPCI	Erasmus MC	Netherlands	2.8M	1996	01/2019
SIDIAP	IDIAP Jordi Gol	Spain	7.8M	2006	12/2018

IPCI – The Netherlands

Integrated Primary Care Information (IPCI), Erasmus University

IPCI is collected from EHR records of patients registered with their GPs throughout the Netherlands. The selection of 391 GPs is representative of the entire country. The database contains records from 1.4 million patients out of a Dutch population of 17M (8.2%) starting in 1996. The median follow-up is 2.2 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity,

dosing directions, strength and indication. The duration of the drug exposure is determined for all drugs in the database by: 1. The amount and dose extracted from the sig or if instruction is "see product instructions" we use the DDD and quantity; 2. Duration available in the record; 3. If option 1 and 2 is not possible we use the DDD derived duration, use the modal duration or default to 30 days dependent on the drug of interest. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board. (Vlug, van der Lei et al. 1999)

Information System for Research in Primary Care (SIDIAP), IDIAP Jordi Gol

SIDIAP is also collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.5M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. For the prescription records the duration is available directly from the EHR system, for dispensing the duration is inferred using the quantity, dosage, and DDD of each drug. Indication diagnoses are available from GP or hospital admission records. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee. (Garcia-Gil Mdel, Hermosilla et al. 2011)

Longitudinal Patient Database (LPD) Belgium (IQVIA)

LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 2.35M patients from a total of 11.5M Belgians (20.4%). The database covers an time period from 2010 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. 61% of the prescriptions contain information about intended duration. For the remaining records, duration can be inferred from package size and signatur information, which is available for 86% of prescriptions. 96.9% of drug exposure records specify the strength of the prescribed product, allowing to calculate daily dose information. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilization studies.

Disease Analyser (DA) Germany (IQVIA).

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes more than 38.7M distinct person records out of at total population of 80M (48.4%) in the country, and collected from 2,734 providers. Patient visiting more than one provider are not cross-identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynecology, 6.2% various Neurology and Psychiatry 7.0% Pediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products containing information about package size, of which

92.% have strength information. 24.9% also contain information about explicit duration. No registration or approval is required for drug utilization studies.

Disease Analyser (DA) France (IQVIA).

DA France consists of data collected from outpatient general practitioner practices and medical centers. Data coverage includes more than 7.1M patients in a population of 67M (10.7%), 2,337 providers practicing at 550 care sites. Patients are not linked across practices. Dates of service include from 2009 through present. Observation time is defined by the first and last consultation dates. Drug information is recorded from prescriptions, which indicate marketed products, all of which come with package size and strength information. 79.6% of the prescriptions also indicate intended days of supply, which allows the calculation of duration and daily dosage. No registration or approval is required for drug utilization studies

IMRD – UK (IQVIA)

IMRD UK is a large database of anonymised electronic medical records collected at Primary Care clinics throughout the UK. Data coverage includes 15.2M patients, 5.6M providers, 793 care sites and more than 5 billion service records, covering 22.5% of a population of 67.5M. Dates of service include from 1996 through present. Quality indicators define the start date for that patient (e.g. each patient's observation period began at the latest of: the patient's registration date, the acceptable mortality recording date of the practice, the Vision date). The end of the observation period is determined by the end date of registration in the database. Drug treatment is recorded as prescriptions, of which 89.3% have a known quantity. Intended duration is only provided in 2.7%, requiring duration to be inferred from the quantity and the parsing the daily signatur provided in 98.7% of the records. Drug strength is known in 69%. All protocols have to be submitted to an independent Scientific Review Committee prior to study conduct.

8.5 Study size

This study is a characterisation of all patient data captured in the data assets and meeting inclusion criteria for exposure to ranitidine and other H_2-receptor antagonists. No hypothesis will be tested. Therefore, sample size calculation for the ability to reject the null hypothesis given an effect size will not be conducted.

Of course, a sufficient number of patients are required for results to be meaningful and projectable to the EU level. Table 2 describes the number of users per H_2-receptor antagonists in the databases based on a count conducted in November 2019 but this number might change based on new available data.

Table 2: Number of patients per H_2-receptor antagonist

	Cimetidine	Famotidine	Nizatidine	Ranitidine	Roxatidine
IPCI	22,754	4,100	1,373	198,763	61
SIDIAP	1,093	8,211	22	329,440	44
LPD BELGIUM	748	0	0	55,977	0
DA FRANCE	5,663	777	103	34,493	0
DA GERMANY	15,641	14,609	3,132	175,828	1,226
IMRD UK	98,236	2,218	34,939	591,504	0

8.6 Data management

The databases used in this study are standardised to the OMOP CDM. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonized. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://github.com/OHDSI/CommonDataModel/wiki and in The Book of OHDSI: http://book.ohdsi.org

For this study we will develop a Drug Utilisation R package that contains all the functionality needed for this study. The R package will be made parameterizable and made available in open source so it can be used for future drug utilisation studies.

Each data partner will execute a Study R package against their database that uses the Drug Utilisation R package to generate the data for the drugs of interests, indications etc. After review of the results the data custodian returns them to the coordinating center (Erasmus MC). The results from all six databases will then be combined in tables and figures for the study report.

8.7 Data analysis

All results will be presented by database. Results pooled over the different databases will be provided for the indication of use and history of renal impairment.

In the Drug Utilisation R package, we will implement the following analyses:

Drug use, both for prevalent and incident users, will be expressed as the number of users per 1,000 persons presented by calendar year, age category (10 years), formulation and sex. (Annex 6 - mock figures 1&2)

The cumulative duration (in days) and expressed as - mean, median, 5, 25, 75, 95 percentiles and minimum, maximum as well as by the number of individuals within the ICH M7 exposure strata (≤ 1 month, >1-12 months, >1-<= 10 years and > 10 years) - will be presented by database and H_2-receptor antagonist ingredient and by treatment class, stratified by gender, age category, formulation and indication. (mock table 1A)

In addition, the cumulative duration of drug exposure (in days) and expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum) will be provided for each database, each indication, each ingredient and each formulation over the complete study period by ICH M7 drug exposure strata, by age category and gender. (mock table 1B)

The cumulative PDD/DDD ratio - expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum as well as by the number of individuals within the ICH M7 exposure strata - will be presented by database and H_2-receptor antagonist ingredient stratified by gender, age category, formulation and indication. Also, the number of patients within different strata of PDD/DDD ratio of the first exposure will be provided and categorized into PDD/DDD ratio <1, PDD/DDD ratio=1 and PDD/DDD ratio >1 (mock table 2A).

In addition, the cumulative PDD/DDD ratio (expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum) will be provided for each data base, each indication, each ingredient and each formulation over the complete study period by ICH M7 drug exposure strata, by age category and gender. (mock table 2B)

The cumulative number of DDDs (expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum) will be presented by database and H_2-receptor antagonist ingredient stratified by gender, age category, formulation and indication. (mock table 3A)

In addition, the cumulative number of DDDs (expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum) will be provided for each data base, each indication, each ingredient and each formulation over the complete study period by ICH M7 drug exposure strata, by age category and gender. (mock table 3B)

The cumulative dose in mg (expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum) will be presented by database and H_2-receptor antagonist ingredient stratified by gender, age category, formulation and indication. (mock table 4A)

In addition, the cumulative dose in mg (expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum) will be provided for each data base, each indication, each ingredient and each formulation over the complete study period by ICH M7 drug exposure strata, by age category and gender. (mock table 4B)

The cumulative annual dose in mg/PY (expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum) will be presented by database and H_2-receptor antagonist ingredient stratified by gender, age category, formulation and indication. (mock table 5A)

In addition, the cumulative annual dose in mg/PY (expressed as mean, median, 5, 25, 75, 95 percentiles and minimum and maximum) will be provided for each data base, each indication, each ingredient and each formulation over the complete study period by ICH M7 drug exposure strata, by age category and gender. (mock table 5B)

The frequencies and proportions for indication of use will be presented for class as a whole and by H_2-receptor antagonist ingredient, stratified by formulation, age category at start of first prescription of the drug of interest (ranitidine or other H_2-receptor antagonist) and sex, presented by database as well as pooled over the databases. (See Annex 6) Patients might have more than one indication for the use of H_2-receptor antagonists e.g. use for both Zollinger Ellison and gastric ulcer thus indication of use is not mutually exclusive. The number of patients having more than one indication will be provided by database.

The frequencies and proportions for chronic renal impairment will be presented for class as a whole and by H_2-receptor antagonist ingredient, presented by database as well as pooled over the databases. (mock table 7)

We will explore a possible analysis on dosage (mg) corrected for body weight in children. The availability of weight measurements is low in the databases and the exposure in children is very limited. Furthermore, if available the measurement has to be close to the drug exposure start date which will reduce the number even further.

As described in 8.3.6.1, the indication of use is determined by the presence of conditions in a period before the start of the drug exposure. We will use the following lookback periods: 180 and 365 days before the first prescription of the H2-receptor antagonist (by class level and ingredient level). The lookback of 180 days will be the main analysis and all tables (see Appendix) including information on the indication of use will be created based on the result of this analysis. In addition, we will investigate how the numbers on the indication of use change when using a look-back of 365 days and this information will be provided in the report. In case of an important change in the percentage of patients with “indication of use” of >25 % additional tables will be provided using the 365 look-back period.

To prevent the identification of individuals, cells containing 1-5 numbers will be suppressed.

The distribution of the observation time will be presented by means of a histogram. In Annex 6, mock tables and figures are presented that can be generated from the aggregated output that is generated locally on the databases.

To make the study results easier accessible we will make them available in an interactive web application that visualises the results for each database.

8.8 Quality control

8.8.1 Data Quality Checks

OHDSI and EHDEN have developed multiple quality control mechanisms for the Common Data Model. These are described in high detail in Chapter 15 of The Book of OHDSI (http://book.ohdsi.org/DataQuality.html).

Data Quality Dashboard Tool

The Data Quality Dashboard (DQD) has been developed in the EHDEN project in close collaboration with OHDSI. It provides a comprehensive, customizable, and transparent way to both evaluate and communicate the quality of an OMOP CDM instance. It provides both the code to run data quality checks against an OMOP CDM instance, as well as visualising the results in a web application.

The data quality checks are organised using the widely accepted Kahn Framework (Kahn, Callahan et al. 2016) for data quality. This groups the checks types in categories: Conformance, Completeness and Plausibility.

- **Conformance** focuses on DQ checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions.
- **Completeness** in the sense of data quality is solely focused on quantifying missingness, or the absence of data.
- **Plausibility** seeks to determine the believability or truthfulness of data values.

Each category has one or more subcategories and are evaluated in two contexts: Validation and Verification.

- **Validation** relates to how well data align with external benchmarks with expectations derived from known true standards.
- **Verification** relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Using the Kahn framework the Data Quality Dashboard takes a systematic-based approach to running data quality checks. Instead of writing thousands of individual checks, we use what we call "data quality check types". These "check types" are more general, parameterized data quality checks into which OMOP tables, fields, and concepts can be substituted to represent a singular data quality idea. For example, one check type might be written as:

> *The number and percent of records with a value in the @cdmFieldName field of the @cdmTableName table less than @plausibleValueLow.*

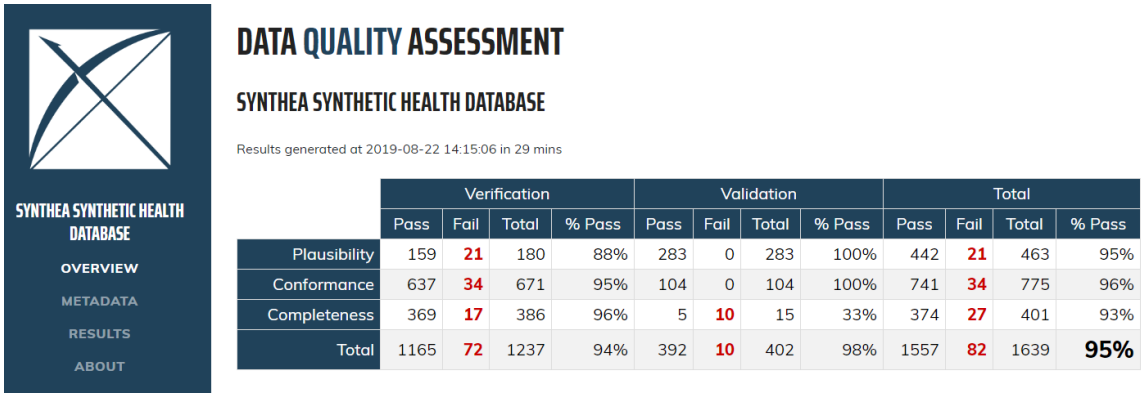
This would be considered a temporal plausibility verification check because we are looking for implausibly low values in some field based on internal knowledge. We can use this check type to substitute in values for *@cdmFieldName*, *@cdmTableName*, and *@plausibleValueLow* to create a unique data quality check. If we apply it to PERSON.YEAR_OF_BIRTH here is how that might look:

*The number and percent of records with a value in the **year_of_birth** field of the **PERSON** table less than **1850**.*

And, since it is parameterized, we can similarly apply it to DRUG_EXPOSURE.days_supply:
*The number and percent of records with a value in the **days_supply** field of the **DRUG_EXPOSURE** table less than **0**.*

In total **3,351 quality control checks** have been implemented in the current version of the tool.

It generates an interactive webtool that provides a high-level overview and a detailed view of the quality checks that have been execute as shown in the figures below on a simulated dataset.



	Verification				Validation				Total			
	Pass	Fail	Total	% Pass	Pass	Fail	Total	% Pass	Pass	Fail	Total	% Pass
Plausibility	159	21	180	88%	283	0	283	100%	442	21	463	95%
Conformance	637	34	671	95%	104	0	104	100%	741	34	775	96%
Completeness	369	17	386	96%	5	10	15	33%	374	27	401	93%
Total	1165	72	1237	94%	392	10	402	98%	1557	82	1639	**95%**

Figure 3: Summary overview of the Data Quality Dashboard

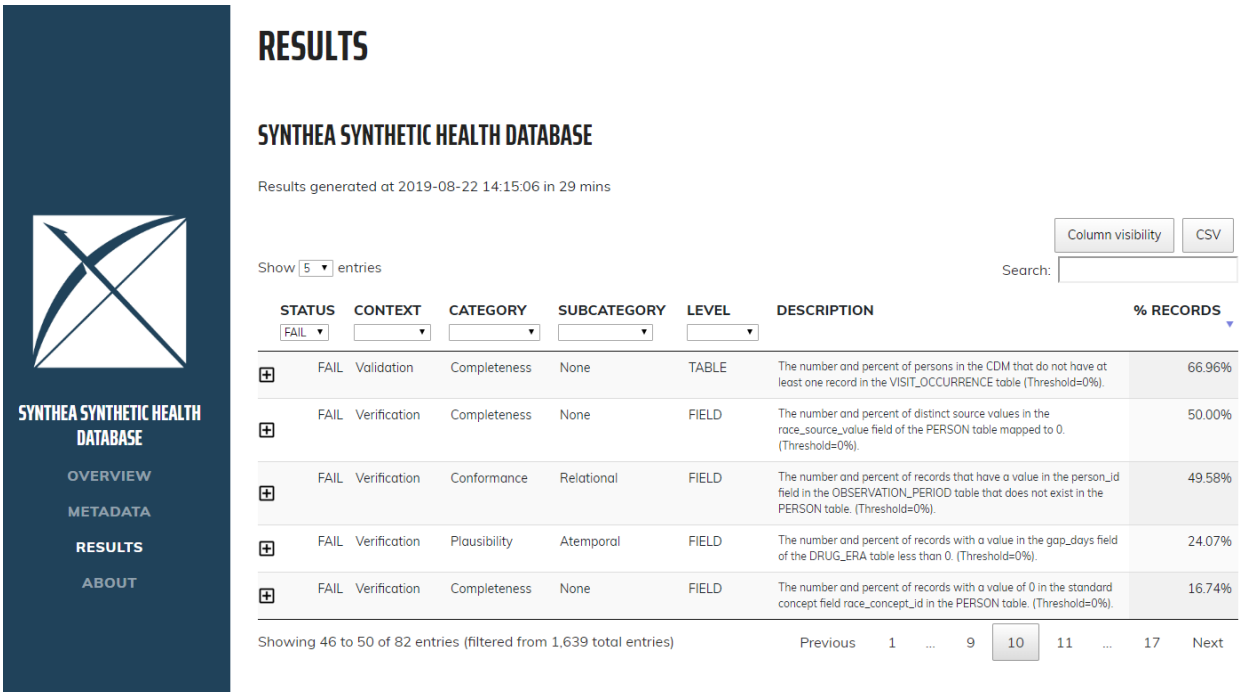


Figure 4: Detailed result view of the Data Quality Dashboard

A further drill-down to the executed query is provided for each check. The DQD will be generated for all the participating data sources.

8.8.2 Code Mapping Validation

We will perform a source code mapping validation step for all data sources in which for each of the concept sets included in the study we will check the mappings of source_code to standard concept_id. This will be done using the checkCohortSourceCodes function in the MethodEvaluation R package. This function uses a cohort definition as created by the ATLAS tool as input, and for each concept set used in the cohort definition it checks which source codes map to the concepts in the set. It also computes the prevalence of these codes over time to help identify temporal issues associated with specific source codes.

In an Annex of the study report, we will add an overview for all the source codes that were mapped to standard concepts used for the indications and chronic renal impairment.

8.8.3 Exposure Duration Characterisation

We will develop and apply an R package that creates a report containing information about the available fields (count and %) in the DRUG_EXPOSURE table, the distinct values per field, and which combinations of fields are available (for example number of patients with days_supply, quantity, and sig). This tool provides quality control information to the data steward on the inferred drug_exposure_end_date during the ETL. For example, the following checks could be made:

1) Compare with the verbatim_end_date if available

2) Check using the days_supply field if available

3) If the quantity and sig are available:
   For solid formulations the quantity in the DRUG_EXPOSURE table denotes the number of distinct units of dispensing (tablets, pills, lozenges etc.), and for liquid formulations the amount of divisible product in the unit provided by the denominator_unit_concept_id of the DRUG_STRENGTH table. This quantity then needs to be divided by the daily dosing instructions provided in the "sig field" of the DRUG_EXPOSURE table to infer the duration. Currently, the "sig field" is not yet modeled into a standard representation and needs to be parsed if needed. For example: '5 tablets, 1 daily", means 5 days of drug_exposure.

4) If the sig is not available but the quantity is, the Defined Daily Dose could be used to get an estimate of the duration. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. (WHO 2012) If the quantity is available the duration can be approximated by:

   Duration = (Quantity * Amount_Value * [amount_unit_concept_id]) / DDD

8.8.4 Software Validity

To assure the proper functionality of the software we will follow the best practices described in Chapter 17 of The Book of OHDSI (http://book.ohdsi.org/SoftwareValidity.html). This includes code review, the addition of unit tests where applicable, source code management, and full code documentation. The analytical pipeline of this study will be made available in opensource for full transparency and replicability.

8.8.5 Benchmark of Ranitidine use

Ranitidine use and use of other H_2-receptor antagonists will be investigated by database which will allow us to benchmark the use between the participating databases, not only overall, but also stratified by age and sex. Furthermore, we will compare the results with other data-sources like publications. Reasons for discrepancies will be investigated to check whether differences are real or related to potential errors and/or biases

8.1 Limitations of the research methods

First, for this study we will use real world data from electronic health care records. There might exist differences between the databases with regard to availability of certain data.

For this study, we are interested in the indication of use of H_2-receptor antagonists (including ranitidine) as well as underlying comorbidity in particular with respect to underlying kidney disease. Both the indication of use as well as underlying comorbidity might be underreported in the source databases.

Second, as low dose ranitidine is also available as an over the counter (OTC) drug, there is the potential of underreporting of ranitidine use. In contrast, as we use prescription and dispensing data, we might overestimate the use of ranitidine (and other H_2-receptor antagonists) as the actual drug intake might be lower.

Third, as we are using primary care databases, use of H_2-receptor antagonists in the Hospital setting is lacking.

Finally, the databases are a subsample of the full population and results should be used with caution when attempting to infer the results nation-wide.

8.2 Other aspects

Not applicable

9 Protection of human subjects

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All the databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the central Remote Research Environment (RRE) of the Erasmus MC. These output files do not contain any data that allow identification of subjects included in the study. The RRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/2016[1] in the various member states.

The protocols will be reviewed by the Institutional Review Boards of the respective databases. As this is a non-interventional observational study, there is no need for ethical approval in the Netherlands, UK, Belgium, Germany and France. For SIDIAP (Spain), both the scientific committee for SIDIAP studies and the local ethics committee will evaluate the protocol before the study can be carried out.

Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (von Elm, Altman et al. 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct'. (Gini, Fournie et al. 2019)

1 REGULATION (EU) 2016/679 - General Data Protection Regulation

10 Management and reporting of adverse events/adverse reactions

According to the new guideline on good pharmacovigilance practice (EMA/873138/2011) there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases).

11 Plans for disseminating and communicating study results

Dissemination activities to be undertaken will have mainly, although not exclusively, a scientific nature (articles, presentations at conferences, etc.).

12 References

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Annex 1. List of stand-alone documents

Documents listed in Annex 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request. Write "None" if there is no document or list documents in a table as indicated below.

Number	Document reference number	Date	Title
1	*Number*	*Date*	*Text*
2	*Number*	*Date*	*Text*
…	*Number*	*Date*	*text*

Annex 2. ENCePP checklist for study protocols

A copy of the ENCePP Checklist for Study protocols available at http://www.encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1: "Study start" means "Start of data collection" "Study progress" means "Progress report(s)" "Study completion" means "End of data collection" "Reporting" means "Final report of the study results"

Annex 3. DRUG_STRENGTH table

The DRUG_STRENGTH table in the Standardized Vocabularies contains structured content about the amount or concentration and associated units of a specific ingredient contained within a drug product. This table contains supplemental information to support standardized analysis of drug utilization and is useful for duration calculation and daily dose assessments as described later in the protocol.

The DRUG_STRENGTH table contains the following relevant fields:

Field	Description
drug_concept_id	A foreign key to the Concept in the CONCEPT table representing the identifier the Clinical Drug Concept.
ingredient_concept_id	The ingredient for which the strength is given.
amount_value	The numeric value associated with the amount of active ingredient for solid formulations.
amount_unit_concept_id	The unit concept for the amount.
numerator_value	The numeric value associated with the concentration of the active ingredient for liquid (or other divisible product, such as ointment, gel, spray, etc.) formulations.
numerator_unit_concept_id	The unit concept for the concentration numerator.
denominator_value	The amount of total liquid.
denominator_unit_concept_id	The unit concept for the concentration denominator.
box_size	The packaging size of the product: The number of units of Clinical of Branded Drug (solid formulation), or the number of vials of Quantified Clinical or Branded Drug (liquid formulation) contained in the marketed box.

For example, for Ranitidine 100 mg Oral Tablet the DRUG_STRENGTH table contains the following information:

Field	Value	Description
drug_concept_id	9611262	“Ranitidine 100 mg Oral Tablet”
ingredient_concept_id	961047	“Ranitidine”
amount_value	100	
amount_unit_concept_id	8576	“MG”
numerator_value	NULL	
numerator_unit_concept_id	NULL	
denominator_value	NULL	
denominator_unit_concept_id	NULL	
box_size	NULL	

In the case of a liquid formulation the numerator and denominator fields are filled in and the amount fields are set to NULL. For example, for Ranitidine 25 MG/ML Injection the DRUG_STRENGTH table contains the following information:

Field	Value	Description

drug_concept_id	1718658	“Ranitidine 25 MG/ML Injection”
ingredient_concept_id	961047	“Ranitidine”
amount_value	NULL	
amount_unit_concept_id	NULL	
numerator_value	25	
numerator_unit_concept_id	8576	“MG”
denominator_value	NULL	
denominator_unit_concept_id	8587	“ML”
box_size	NULL	

For more detailed information about the DRUG_STRENGTH table we refer to: https://github.com/OHDSI/CommonDataModel/wiki

Annex 4. Concept Sets

Below the concept sets are presented that are used in the study for the indications of drug use and the Renal Impairment. These lists include all the children in the hierarchy of the parent code (first concept in the list). Note that many of these more specific codes may not be present in the databases (see the quality control section for more details).

Table A1: Concept set for GERD

concept_id	concept_name	concept_code
318800	Gastroesophageal reflux disease	235595009
4046097	Sandifer syndrome	230314007
4076267	Gastro-esophageal reflux disease with ulceration	245754007
765110	Diaphragmatic hernia with gastroesophageal reflux disease	15926471000119109
42535063	Gastroesophageal reflux disease in pregnancy	15643101000119103
36687117	Paraesophageal hernia with gastroesophageal reflux disease	15926411000119101
36713493	Erosive gastro-esophageal reflux disease	717847008
4144111	Gastroesophageal reflux disease without esophagitis	266435005
36712969	Neonatal gastroesophageal reflux	15749591000119107
36712768	Gastroesophageal reflux in child	10999201000119106
36713492	Non-erosive gastro-esophageal reflux disease	717846004
4159148	Gastroesophageal reflux disease with apnea	371101003
4159156	Gastroesophageal reflux disease with hiatal hernia	371132002

Table A2: Concept set for Zollinger Ellison Syndrome

concept_id	concept_name	concept_code
4200399	Zollinger-Ellison syndrome	53132006
36713527	Gastric ulcer due to Zollinger-Ellison syndrome	717891008
36717645	Duodenal ulcer due to Zollinger-Ellison syndrome	717892001

Table A3: Concept set for Gastric Ulcer

concept_id	concept_name	concept_code
4265600	Gastric ulcer	397825006
45763550	Antral ulcer	4911000119101
4248429	Gastric ulcer without hemorrhage AND without perforation	73481001
36716880	Gastric ulcer caused by chemical	723105009
4080599	Gastrocolic ulcer	24060004
4341234	Gastric erosion	235651006
44808499	Gastric ulcer with obstruction	849591000000103
4197099	Combined gastric AND duodenal ulcer	79806007
4319441	Acute gastric ulcer	95529005
4049466	Gastric ulcer with hemorrhage	15902003
37017373	Gastric ulcer caused by drug	713638002
4027942	Esophagogastric ulcer	10699001
42572805	Erosion of gizzard	341851000009107
4059178	Gastrojejunal ulcer	16121001
37119136	Ulcer of stomach due to lymphocytic gastritis	724521003
42538546	Infection causing ulcer of stomach	762274007
45757242	Erosive gastritis	1086791000119100
37110307	Ulcer of stomach due to eosinophilic gastritis	724520002
4197598	Multiple gastric ulcers	313425006
36716879	Gastric ulcer caused by ionizing radiation	723104008
4340787	Healed gastric ulcer	235702004
4331322	Prepyloric ulcer	22620000
4189591	Pyloric ulcer	39204006
36717606	Gastric ulcer caused by fungus	723101000
4318534	Chronic gastric ulcer	95530000

36716877	Gastric ulcer due to parasitic infection	723102007
36713527	Gastric ulcer due to Zollinger-Ellison syndrome	717891008
4321586	Gastric ulcer with perforation	9829001
36716876	Gastric ulcer caused by virus	723100004
36716875	Gastric ulcer caused by bacterium	723099007
195851	Gastric ulcer without hemorrhage, without perforation AND without obstruction	59913009
4028243	Chronic gastrojejunal ulcer	128288009
4266523	Gastric ulcer with hemorrhage AND perforation	62366003
44791257	Non-steroidal anti-inflammatory drug induced gastric ulcer	248891000000103
4211001	Chronic gastric ulcer with hemorrhage	57246001
4057953	Acute gastric ulcer with perforation	19850005
4057076	Healed gastric ulcer leaving a scar	196775009
4223226	Gastric ulcer with perforation but without obstruction	84038009
4195231	Acute gastric ulcer without hemorrhage AND without perforation	67964002
4101104	Gastrojejunal ulcer without hemorrhage AND without perforation	2783007
36716878	Gastric ulcer caused by alcohol	723103002
4342642	Chronic drug-induced ulcer of stomach	235650007
4341233	Acute drug-induced ulcer of stomach	235648004
44808503	Gastrojejunal ulcer with obstruction	849621000000100
4087594	Acute gastric mucosal erosion	18665000
4341235	Multiple gastric erosions	235652004
45757062	Gastric ulcer due to Helicobacter pylori	103691000119106
4188456	Stress ulcer of stomach	415624002
4076267	Gastro-esophageal reflux disease with ulceration	245754007
198190	Gastric ulcer with perforation AND obstruction	72486001
45757397	Gastric ulcer caused by non-steroidal anti-inflammatory drug in therapeutic use	129141000119104
4025501	Acute gastric ulcer with obstruction	196632005
4102254	Gastroesophageal erosion	301007008
4150681	Chronic gastric ulcer with perforation	31301004
4231580	Acute gastric ulcer with hemorrhage	89748001
40481540	Acute erosive gastritis	444926003
764846	Gastric ulcer caused by cytomegalovirus	689991000119100
4041707	Gastric ulcer with hemorrhage but without obstruction	16694003
4055895	Chronic gastric ulcer with obstruction	196639001
4296611	Chronic gastric ulcer without hemorrhage AND without perforation	76796008
4024984	Acute gastrojejunal ulcer	196707000
4271442	Chronic erosive gastritis	63137003
37110309	Anastomotic ulcer of stomach caused by drug	724523000
4006992	Acute gastric erosion associated with drug ingestion	111350000
4143871	Bleeding gastric erosion	307233002
4310838	Gastric ulcer induced by anti-platelet agent	424301005
4222477	Gastrojejunal ulcer with hemorrhage	84124004
196443	Gastric ulcer without hemorrhage AND without perforation but with obstruction	31452001
4232767	Helicobacter-associated pyloric ulcer	89662003
4207217	Gastric ulcer with hemorrhage AND obstruction	53877005
4147351	Gastrojejunal ulcer with perforation	30183003
4179773	Gastrojejunal ulcer with hemorrhage but without obstruction	50663005
37110308	Anastomotic ulcer of stomach caused by Helicobacter pylori	724522005
433515	Chronic gastrojejunal ulcer with hemorrhage	62838000
4024985	Acute gastrojejunal ulcer with obstruction	196712004
4273874	Gastrojejunal ulcer with hemorrhage AND perforation	64094003
4169592	Acute gastric ulcer with hemorrhage AND perforation	48974009
4001167	Acute ulcerative gastroenteritis complicating pneumonia	109814008
4101870	Chronic gastrojejunal ulcer with perforation	2807004

438188	Gastrojejunal ulcer without hemorrhage AND without perforation but with obstruction	47152002
197914	Chronic gastric ulcer with perforation but without obstruction	36246001
4177387	Chronic gastrojejunal ulcer without hemorrhage AND without perforation	4269005
4205670	Bleeding stress ulcer of stomach	308882008
195583	Chronic gastric ulcer without hemorrhage AND without perforation but with obstruction	60531007
438795	Chronic gastrojejunal ulcer without hemorrhage, without perforation AND without obstruction	41626001
4294973	Chronic gastric ulcer with hemorrhage AND with perforation	76181002
42538071	Cushing ulcer of stomach	738791006
4024986	Chronic gastrojejunal ulcer with obstruction	196719008
4147683	Acute gastrojejunal ulcer without hemorrhage AND without perforation	30514008
4274491	Acute gastrojejunal ulcer with hemorrhage	63954007
199062	Acute gastric ulcer without hemorrhage, without perforation AND without obstruction	54053008
192954	Acute gastric ulcer without hemorrhage AND without perforation but with obstruction	81225008
193795	Acute gastric ulcer with hemorrhage but without obstruction	70418001
200769	Chronic gastric ulcer without hemorrhage, without perforation AND without obstruction	1567007
197018	Chronic gastric ulcer with hemorrhage but without obstruction	76078009
4038489	Gastrojejunal ulcer with perforation but without obstruction	11818002
200137	Acute gastric ulcer with perforation AND obstruction	43694004
4069766	Gastrojejunal ulcer with perforation AND obstruction	21759003
4071203	Gastric ulcer with hemorrhage AND perforation but without obstruction	2066005
4280942	Acute gastrojejunal ulcer with perforation	66636001
36683388	Curling's ulcer of stomach	781203005
4069838	Gastric ulcer with hemorrhage, with perforation AND with obstruction	17593008
198467	Acute gastric ulcer with hemorrhage AND obstruction	46708007
201885	Chronic gastric ulcer with hemorrhage AND with obstruction	85859006
4175673	Gastrojejunal ulcer with hemorrhage AND obstruction	42698006
37110306	Gastric ulcer caused by Helicobacter pylori and non-steroidal anti-inflammatory agent	724519008
194680	Acute gastric ulcer with perforation but without obstruction	90628007
4206315	Chronic gastric ulcer with perforation AND with obstruction	55483002
439858	Gastrojejunal ulcer without hemorrhage, without perforation AND without obstruction	35517004
4244406	Chronic gastrojejunal ulcer with hemorrhage but without perforation	59356009
437598	Acute gastrojejunal ulcer with perforation but without obstruction	72395008
195845	Acute gastric ulcer with hemorrhage, with perforation AND with obstruction	53337006
4183005	Gastrojejunal ulcer with hemorrhage, with perforation AND with obstruction	54798007
432951	Acute gastrojejunal ulcer without hemorrhage AND without perforation but with obstruction	10389003
4217947	Acute gastrojejunal ulcer with hemorrhage AND perforation	81387001
436729	Chronic gastrojejunal ulcer with hemorrhage AND obstruction	90257004
196442	Chronic gastric ulcer with hemorrhage AND with perforation but without obstruction	74341002
4164920	Chronic gastrojejunal ulcer with hemorrhage AND perforation	45640006
436460	Acute gastrojejunal ulcer without hemorrhage, without perforation AND without obstruction	77987006
198801	Chronic gastric ulcer with hemorrhage, with perforation AND with obstruction	85787009
435579	Chronic gastrojejunal ulcer with perforation but without obstruction	62477005
434400	Chronic gastrojejunal ulcer without hemorrhage AND without perforation but with obstruction	56579005

4336971	Gastrojejunal ulcer with hemorrhage AND with perforation but without obstruction	87796008
441063	Acute gastrojejunal ulcer with hemorrhage AND obstruction	72408002
444102	Chronic gastrojejunal ulcer with perforation AND with obstruction	10897002
199855	Acute gastric ulcer with hemorrhage AND with perforation but without obstruction	17067009
438468	Acute gastrojejunal ulcer with hemorrhage but without obstruction	59515005
435846	Acute gastrojejunal ulcer with perforation AND obstruction	72219001
441328	Acute gastrojejunal ulcer with hemorrhage AND with perforation but without obstruction	66673003
442314	Acute gastrojejunal ulcer with hemorrhage, with perforation AND with obstruction	58711008
443779	Chronic gastrojejunal ulcer with hemorrhage, with perforation AND with obstruction	24001002
437326	Chronic gastrojejunal ulcer with hemorrhage AND with perforation but without obstruction	46523000

Table A4: Concept set for Duodenal Ulcer

concept_id	**concept_name**	**concept_code**
4198381	Ulcer of duodenum	51868009
4194177	Familial hypergastrinemic duodenal ulcer	6761005
4105935	Duodenal ulcer with increased serum pepsinogen I	29755007
4024842	Recurrent duodenal ulcer	196671008
42538548	Ulcer of duodenum due to infection	762276009
44808500	Duodenal ulcer with obstruction	849601000000109
4209746	Duodenal ulcer without hemorrhage AND without perforation	56776001
4340230	Duodenal erosion	235692002
4296319	Normopepsinogenemic familial duodenal ulcer	76338009
4285720	Giant duodenal ulcer	68834009
4099014	Duodenal ulcer with hemorrhage	27281001
37203820	Tremor, nystagmus, duodenal ulcer syndrome	782935003
4299937	Postpyloric ulcer	78054007
37110319	Duodenal ulcer caused by fungus	724534002
4229614	Duodenal ulcer with perforation	88968005
37117196	Duodenal ulcer caused by ionizing radiation	724531005
4028242	Chronic duodenal ulcer	128286008
4182589	Childhood duodenal ulcer	43035002
36717645	Duodenal ulcer due to Zollinger-Ellison syndrome	717892001
37110315	Duodenal ulcer caused by drug	724529001
4057053	Acute duodenal ulcer	196652006
36713516	Eosinophilic duodenal ulcer	717878007
4197099	Combined gastric AND duodenal ulcer	79806007
37110317	Ulcer of duodenum caused by chemical	724532003
37110318	Duodenal ulcer caused by virus	724533008
36713517	Lymphocytic duodenal ulcer	717879004
37117176	Duodenal ulcer caused by bacterium	723884008
4040644	Familial duodenal ulcer associated with rapid gastric emptying	16516008
4149010	Duodenal ulcer with hemorrhage but without obstruction	35560008
4342649	Stress ulcer of duodenum	235688009
4174560	Duodenal ulcer induced by anti-platelet agent	423643000
4265479	Acute duodenal ulcer with perforation	61347001
4138962	Acute duodenal ulcer without hemorrhage AND without perforation	32490005
4084844	Duodenal ulcer with hemorrhage AND obstruction	18367003
36716253	Duodenal ulcer caused by non-steroidal anti-inflammatory drug	722200003
435305	Duodenal ulcer without hemorrhage AND without perforation but with obstruction	18169007
4315039	Duodenal ulcer with perforation but without obstruction	86983005
4027729	Acute duodenal ulcer with hemorrhage	12847006

4298227	Duodenal ulcer with perforation AND obstruction	77410006
438469	Duodenal ulcer without hemorrhage, without perforation AND without obstruction	34580000
4173408	Chronic duodenal ulcer with perforation	49916007
4222896	Chronic duodenal ulcer without hemorrhage AND without perforation	40214005
4214461	Acute erosion of duodenum	39344002
4024840	Acute duodenal ulcer with obstruction	196658005
436453	Chronic duodenal ulcer with obstruction	196666001
37110314	Duodenal ulcer caused by Helicobacter pylori	724528009
4232181	Chronic duodenal ulcer with hemorrhage	89469000
4031954	Duodenal ulcer with hemorrhage AND perforation	23812009
436148	Chronic duodenal ulcer with hemorrhage but without obstruction	62341002
437323	Chronic duodenal ulcer with hemorrhage AND obstruction	34021006
432354	Chronic duodenal ulcer with perforation but without obstruction	34602004
443770	Chronic duodenal ulcer without hemorrhage AND without perforation but with obstruction	28082003
441062	Acute duodenal ulcer with hemorrhage AND obstruction	87756006
4336230	Acute duodenal ulcer with hemorrhage AND perforation	86895006
435578	Acute duodenal ulcer with perforation but without obstruction	22511002
4341240	Cushing ulcer of duodenum	235689001
435859	Acute duodenal ulcer without hemorrhage AND without perforation but with obstruction	75342000
440755	Acute duodenal ulcer without hemorrhage, without perforation AND without obstruction	23693000
434402	Acute duodenal ulcer with hemorrhage but without obstruction	66767006
433246	Chronic duodenal ulcer without hemorrhage, without perforation AND without obstruction	57940000
4035167	Duodenal ulcer with hemorrhage AND with perforation but without obstruction	15115006
4049270	Duodenal ulcer with hemorrhage, with perforation AND with obstruction	12355008
439058	Chronic duodenal ulcer with perforation AND obstruction	60551006
4289830	Chronic duodenal ulcer with hemorrhage AND perforation	36975000
37110316	Duodenal ulcer caused by Helicobacter pylori and non-steroidal anti-inflammatory agent	724530006
4342650	Curling's ulcer of duodenum	235690005
434070	Acute duodenal ulcer with perforation AND obstruction	62936002
437021	Acute duodenal ulcer with hemorrhage, with perforation AND with obstruction	41986000
440756	Chronic duodenal ulcer with hemorrhage, with perforation AND with obstruction	86258000
438796	Chronic duodenal ulcer with hemorrhage AND with perforation but without obstruction	81142005
435855	Acute duodenal ulcer with hemorrhage AND with perforation but without obstruction	51847008

Table A1: Concept set for Chronic Renal Impairment

concept_id	**concept_name**	**concept_code**
192359	Renal failure syndrome	42399005
4033463	Enamel-renal syndrome	109477002
443919	Hypertensive renal failure	49220004
37017425	Renal failure syndrome co-occurrent with human immunodeficiency virus infection	713696000
193782	End-stage renal disease	46177005
4150547	Anemia secondary to renal failure	310647000
4153876	Renal failure as a complication of care	269301005
198185	Chronic renal failure	90688005
196455	Hepatorenal syndrome	51292008
4030520	End stage renal failure on dialysis	236435004

4128200	End stage renal failure untreated by renal replacement therapy	236434000
443961	Anemia of chronic renal failure	49708008
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	194781004
439695	Hypertensive heart and renal disease with renal failure	194780003
4125970	End stage renal failure with renal transplant	236436003
4322556	Chronic progressive renal failure	425369003
37018886	End stage renal disease due to hypertension	111411000119103
36679002	Hyperuricemia, pulmonary hypertension, renal failure, alkalosis syndrome	776416004
44784439	Benign hypertensive renal disease with renal failure	698591006
45768813	Anemia in end stage renal disease	707324008
4128067	Acute-on-chronic renal failure	236433006
4200639	Post-renal renal failure	301814009
4126427	Pulmonary renal syndrome	236432001
45769906	End stage renal disease on dialysis due to type 2 diabetes mellitus	90791000119104
42872405	Anemia, pre-end stage renal disease on erythropoietin protocol	1801000119106
44782717	End stage renal disease on dialysis due to hypertension	153891000119101
762973	Hypertensive end stage renal disease	434431000124103
43020455	Malignant hypertensive end stage renal disease	285841000119104
45769904	End stage renal disease on dialysis due to type 1 diabetes mellitus	90771000119100
45772751	Hypertension concurrent and due to end stage renal disease on dialysis	704667004
46273164	End stage renal disease due to benign hypertension	712487000
45757393	Hypertension concurrent and due to end stage renal disease on dialysis due to type 1 diabetes mellitus	128001000119105
43021864	Malignant hypertensive end stage renal disease on dialysis	286371000119107
45757392	Hypertension concurrent and due to end stage renal disease on dialysis due to type 2 diabetes mellitus	127991000119101

Annex 5. DDD of H_2-receptor antagonist ingredients

Ingredient	**DDD_{oral}**	**$DDD_{parenteral}$**
Ranitidine	0.3 g	0.3 g
Cimetidine	0.8 g	0.8 g
Famotidin	0.04 g	0.04 g
Nizatidine	0.3 g	0.3 g
Niperotidine	Unknown	
Roxatidine	0.15 g	Not available as parenteral administration
Ranitidine bismuth citrate	0.8 g	Not available as parenteral administration
Lafutidine	0.02 g	Not available as parenteral administration

Annex 6. Mock figures and tables

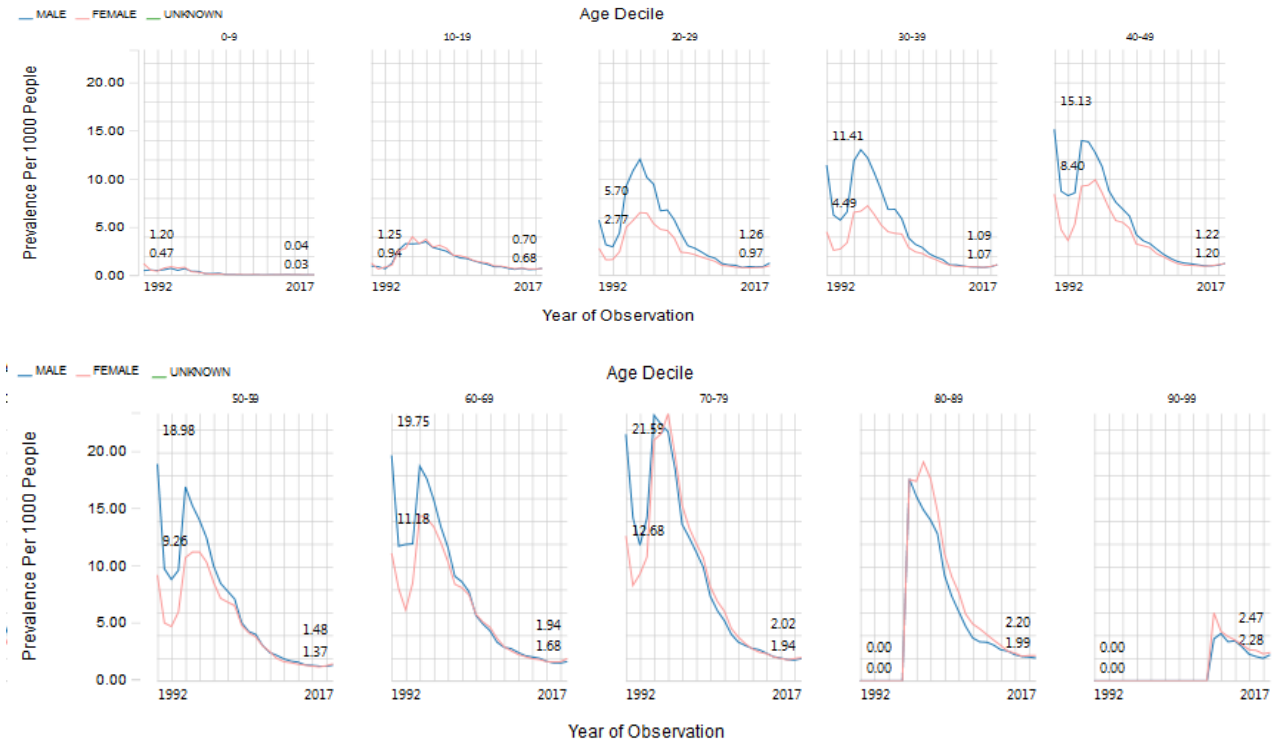

Figure 1: Incidence / prevalence of drug use (per database, by calendar year, gender and per age category)

We will also provide incidence/prevalence of drug use zoomed in to the **last 5 years** (to give more actual drug use especially as use of H_2-receptor antagonists decreased over time because of PPI) This figure can be added in an interactive dashboard that allows moving over the curve to get the exact numbers.

Note that Figure 1 shows as example the prevalence of the number of drug exposure starts by calendar year, age group and gender in the "DA Germany" database for Ranitidine. We will make a new version of this using the prevalence calculation described in the protocol.

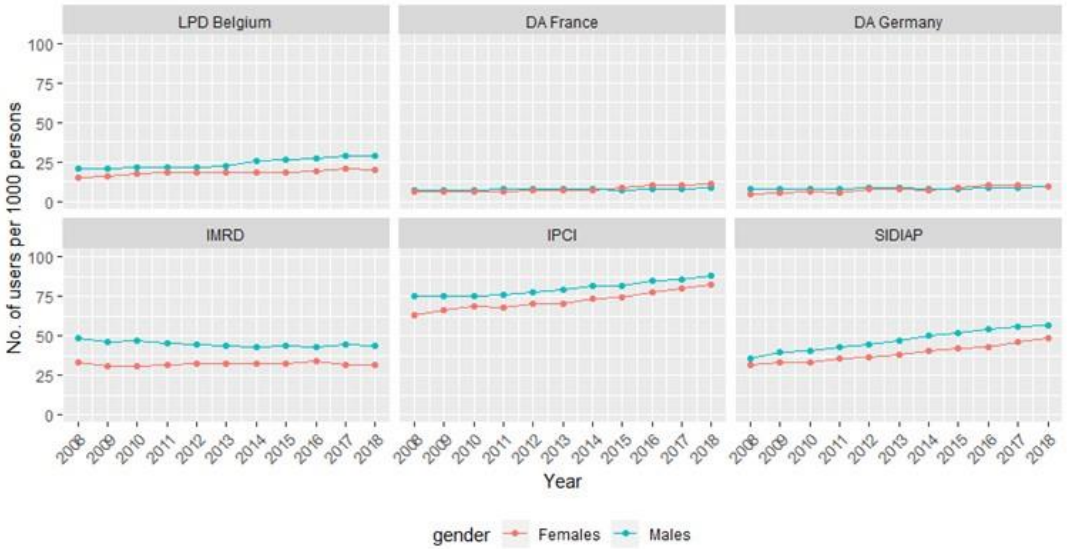

Figure 2: Incidence / prevalence of drug use (per database, by calendar year)

Figure 3: For each data base, each indication, each ingredient, each formulation, and each age category, the **Cumulative number of treatment days** (= cumulative drug exposure duration) over the complete study period will be presented as **boxplots** by drug exposure duration strata.

Figure 4: For each data base, each indication, each ingredient, each formulation, and each age category, PDD/DDD will be presented as **boxplots** (per database, by ingredient)

Figure 5: For each data base, each indication, each ingredient, each formulation, and each age category, cumulative number of DDDs over the complete study period will be presented as **boxplots** (per database, by ingredient)

Figure 6: For each data base, each indication, each ingredient, each formulation, and each age category, cumulative dose in mg over the complete study period will be presented as **boxplots** (per database, by ingredient)

Data from these figures will also be made available in tabular format if this is not already available in the tables described below. Plots will be only generated if relevant but all data will be available in the tables

Table 1A: Cumulative duration of drug exposure (in days) over the complete study period

		DA France[#]												
		N users	Mean	Median	P5	Q1	Q3	P95	Min	Max	Number of patients within the different ICH M7 exposure strata			
											<= 1 month	>1-12 months	>1-≤ 10 years	>10 years
Ranitidine*														
Gender	Males													
	Females													
Age category	small children[§]													
	children[§]													
	adolescent[§]													
	19-30													
	30-40													
	40-50													
	50-60													
	60-70													
	70-80													
	>80													
Additional age category	<18 years													
	18-<75 years													
	>= 75 years													
Oral formulation														
Parenteral formulation														
Indication of use	GERD													
	Gastric or duodenal ulcer													

		DA France[#]												
		N users	Mean	Median	P5	Q1	Q3	P95	Min	Max	Number of patients within the different ICH M7 exposure strata			
											<= 1 month	>1-12 months	>1-≤ 10 years	>10 years
	Zollinger Ellison Syndrome													
	Unknown													

#: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD, Belgium, SIDIAP and IMRD

* Data will be provided, for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate, lafutidine, and for the treatment class

§ ICH age categories: (small children (< 2 years); children (2 to 11 years); adolescents (12 to-18 years).

Table 1B: Cumulative duration of drug exposure (days) over the complete study period by ICH M7 drug exposure strata, age category and gender presented for each data base, each indication, each ingredient and each formulation

			DA France/GERD/Ranitidine/oral #								
				cumulative duration of drug exposure							
			N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
Cumulative Drug Exposure Duration strata∞	Age category	Gender									
0 - <=1 Month	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-12 months	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									

			DA France/GERD/Ranitidine/oral #								
				cumulative duration of drug exposure							
			N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
		Females									
	All age category	Total									
		Males									
		Females									
>1-≤ 10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									

			DA France/GERD/Ranitidine/oral #								
				cumulative duration of drug exposure							
			N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
	All age category	Total									
		Males									
		Females									
Cumulative Drug Exposure Duration Overall	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									

[#]: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD and for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate, lafutidine, and for the treatment class, by indication and by formulation

∞ Cumulative duration of H_2-receptor antagonist exposure stratified (thus in this example ranitidine exposure) according to ICH M7 .

Table 2A: PDD/DDD Ratio

		DA France[#]											
		N users	Mean	Median	P5	Q1	Q3	P95	Min	Max	Number of patients within the different PDD/DDD strata		
											<1[Ω]	= 1 [Ω]	> 1[Ω]
Ranitidine*													
Gender	Males												
	Females												
Age category	small children[§]												
	children[§]												
	adolescents[§]												
	19-30												
	30-40												
	40-50												
	50-60												
	60-70												
	70-80												
	>80												
Additional age category	<18 years												
	18-<75 years												
	>= 75 years												
Oral formulation													
Parenteral formulation													
Indication of use	GERD												
	Gastric or duodenal ulcer												
	Zollinger Ellison Syndrome												
	Unknown												

#: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD

*Data will be provided, for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate and lafutidine

§ ICH age categories: (small children (< 2 years); children (2 to 11 years); adolescents (12 to-18 years).

Ω number of patients within the three PDD/DDD strata (<1,1 and >1) are provided for the first exposure of the individual ingredients

Table 2B: PDD/DDD Ratio over the complete study period by ICH M7 drug exposure strata, age category and gender presented for each data base, each indication, each ingredient and each formulation

			DA France/GERD/Ranitidine/oral[#]								
			N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
Cumulative Drug Exposure Duration strata[∞]	Age category	Gender									
0 - <=1 Month	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-12 months	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									

			DA France/GERD/Ranitidine/oral[#]								
			N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-≤ 10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									

			DA France/GERD/Ranitidine/oral[#]								
			N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
		Females									
	All age category	Total									
		Males									
		Females									
Cumulative Drug Exposure Duration Overall	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									

[#]: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD and for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate and lafutidine, by indication and by formulation

∞ Cumulative duration of H_2-receptor antagonist exposure of interest (thus in this example ranitidine exposure) stratified according to ICH M7

Table 3A: Cumulative number of DDDs over the complete study period

			DA France[#]							
		N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
Ranitidine*										
Gender	Males									
	Females									
Age category	small children[§]									
	children[§]									
	adolescents[§]									
	19-30									
	30-40									
	40-50									
	50-60									
	60-70									
	70-80									
	>80									
Additional age category	<18 years									
	18-<75 years									
	>= 75 years									
Oral formulation										
Parenteral formulation										
Indication of use	GERD									
	Gastric or duodenal ulcer									
	Zollinger Ellison Syndrome									
	Unknown									

#: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD

*Data will be provided, for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate and lafutidine

§ ICH age categories: (small children (< 2 years); children (2 to 11 years); adolescents (12 to-18 years).

Table 3B: Cumulative drug exposure (DDD) over the complete study period by ICH M7 drug exposure strata, age category and gender presented for each data base, each indication, each ingredient and each formulation

			DA France/GERD/Ranitidine/oral #								
				cumulative drug exposure in DDD							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
Cumulative Drug Exposure Duration strata∞	Age category	Gender									
0 - <=1 Month	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-12 months	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									

			DA France/GERD/Ranitidine/oral #								
				cumulative drug exposure in DDD							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-≤ 10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									

			DA France/GERD/Ranitidine/oral #								
				cumulative drug exposure in DDD							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
Cumulative Drug Exposure Duration Overall	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									

[#]: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD and for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate and lafutidine, by indication and by formulation

∞ Cumulative duration of H_2-receptor antagonist exposure (thus in this example ranitidine exposure) stratified according to ICH M7

Table 4A: Cumulative dose in mg over the complete study period

		DA France[#]								
		N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
Ranitidine*										
Gender	Males									
	Females									
Age category	small children									
	children									
	adolescents									
	19-30									
	30-40									
	40-50									
	50-60									
	60-70									
	70-80									
	>80									
Additional age category	<18 years									
	18-<75 years									
	>= 75 years									
Oral formulation										
Parenteral formulation										
Indication of use	GERD									
	Gastric or duodenal ulcer									
	Zollinger Ellison Syndrome									

	Unknown									

#: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD

*Data will be provided, for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate, lafutidine

§ ICH age categories: (small children (< 2 years); children (2 to 11 years); adolescents (12 to-18 years)

Table 4B: Cumulative drug exposure (mg) over the complete study period by ICH M7 drug exposure strata, age category and gender presented for each data base, each indication, each ingredient and each formulation

			DA France/GERD/Ranitidine/oral #								
				cumulative drug exposure in mg							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
Cumulative Drug Exposure Duration strata∞	Age category	Gender									
0 - <=1 Month	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-12 months	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									

			DA France/GERD/Ranitidine/oral #								
				cumulative drug exposure in mg							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-≤ 10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									

			DA France/GERD/Ranitidine/oral #								
				cumulative drug exposure in mg							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
Cumulative Drug Exposure Duration Overall	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									

[#]: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD and for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate, and lafutidine by indication and by formulation

∞ Cumulative duration of H_2-receptor antagonist exposure (thus in this example ranitidine exposure) stratified according to ICH M7

Table 5A: Cumulative annual dose (mg/PY) over the complete study period

		DA France[#]								
		N users	Mean	Median	P5	Q1	Q3	P95	Min	Max
Ranitidine*										
Gender	Males									
	Females									
Age category	small children									
	children									
	adolescents									
	19-30									
	30-40									
	40-50									
	50-60									
	60-70									
	70-80									
	>80									
Additional age category	<18 years									
	18-<75 years									
	>= 75 years									
Oral formulation										
Parenteral formulation										
Indication of use	GERD									
	Gastric or duodenal ulcer									
	Zollinger Ellison Syndrome									

	Unknown									

#: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD

*Data will be provided, for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate, lafutidine

§ ICH age categories: (small children (< 2 years); children (2 to 11 years); adolescents (12 to-18 years)

Table 5B: Cumulative annual dose (mg/PY) over the complete study period by ICH M7 drug exposure strata, age category and gender presented for each data base, each indication, each ingredient and each formulation

			DA France/GERD/Ranitidine/oral #								
				cumulative annual dose (mg/PY)							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
Cumulative Drug Exposure Duration strata∞	Age category	Gender									
0 - <=1 Month	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-12 months	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									

			DA France/GERD/Ranitidine/oral #								
				cumulative annual dose (mg/PY)							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>1-≤ 10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
>10 years	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									

			DA France/GERD/Ranitidine/oral #								
				cumulative annual dose (mg/PY)							
			N users								
				Mean	Median	P5	Q1	Q3	P95	Min	Max
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									
Cumulative Drug Exposure Duration Overall	0-<18 years	Total									
		Males									
		Females									
	18-<75 years	Total									
		Males									
		Females									
	>= 75 years	Total									
		Males									
		Females									
	All age category	Total									
		Males									
		Females									

[#]: Data will not only be presented for France but also for all other participating databases thus also for DA Germany, IPCI, LPD Belgium, SIDIAP and IMRD and for all individual ingredients thus also for cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate, and lafutidine by indication and by formulation

∞ Cumulative duration of H_2-receptor antagonist exposure (thus in this example ranitidine exposure) stratified according to ICH M7

Table 6: Indication of use per ingredient

			DA France	DA Germany	IPCI	LPD Belgium	SIDIAP	IMRD	Pooled
			N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
H_2-receptor antagonist_class	Age-strata								
	0-<18 years	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class	18-<75 years	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class	>= 75 years	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class	Total	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class	Gender								
	Males	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class	Females	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class_oral	Age-strata								
	0-<18 years	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							

		Unknown							
H_2-receptor antagonist_class_oral	18-<75 years	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class_oral	>= 75 years	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class_oral	Total	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class_oral	Gender								
	Males	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
H_2-receptor antagonist_class_oral	Females	GERD							
		Gastric or duodenal ulcer							
		Zollinger Ellison Syndrome							
		Unknown							
etc.*									

*Data will be provided, not only for H_2receptor antagonist as class but also for all individual ingredients thus also for ranitidine, cimetidine, famotidine, nizatidine, niperotidine, roxatidine, ranitidine bismuth citrate, lafutidine.
For these individual ingredients, the indication of use will also be provided by type of formulation (oral or parenteral) if both formulations are available (see also Annex 4 - list of H_2-receptor antagonists with DDD)

Table 7: History of renal impairment in patients treated with ranitidine

	DA France	DA Germany	IPCI	LPD Belgium	SIDIAP	IMRD	Pooled
H2-receptor antagonist_class (total number of users)							
Renal impairment N(%)							
Ranitidine users (total number of users)							
Renal impairment N (%)							
Cimetidine users (total number of users)							
Renal impairment N (%)							
Famotidine users (total number of users)							
Renal impairment N (%)							
Nizatidine users (total number of users)							
Renal impairment N (%)							
Niperotidine users (total number of users)							
Renal impairment N (%)							
Roxatidine users (total number of users)							
Renal impairment N (%)							
Ranitidine bismuth citrate (total number of users)							
Renal impairment N (%)							
Lafutidine users (total number of users)							
Renal impairment N (%)							