Study of exposure and use patterns of alternatives to ranitidine-containing medicines in patients treated with ranitidine

EMA/2017/09/PE (LOT 4)

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Protocol Approval and Sign-off

I confirm that I have read the contents of this protocol and its attachments. I approve the protocol in its current form.

			16 September 2021
Principal Investigator	Katia Verhamme		
	Print name, title here	Signature	Date
Senior QC	Deborah Layton		16 September 2021
	Print name, title here	Signature	Date

PASS Information

Section	Description
Title	Study of exposure and use patterns of alternatives to ranitidine-containing medicines in patients treated with ranitidine
Protocol version identifier	Draft version 0.1
Date of last version of protocol	*NA*
EU PAS register number	To be registered
Active substance	**H2RA** A02BA01 Cimetidine A02BA02 Ranitidine A02BA03 Famotidine A02BA04 Nizatidine A02BA05 Niperotidine A02BA06 Roxatidine A02BA08 Lafutidine A02BA51 Cimetidine combinations A02BA53 Famotidine combinations **PPI** A02BC01 Omeprazole A02BC02 Pantoprazole A02BC03 Lansoprazole A02BC04 Rabeprazole A02BC05 Esomeprazole A02BC06 Dexlansoprazole A02BC07 Dexrabeprazole A02BC08 Vonoprazan A02BC53 Lansoprazole, combinations **Antacids** A02AA Magnesium compounds A02AB Aluminium compounds A02AC Calcium compounds A02AD Combinations and complexes of aluminium, calcium and magnesium compounds A02AF Antacids with antiflatulents A02AG Antacids with antispasmodics A02AH Antacids with sodium bicarbonate A02AX Antacids, other combinations **Other drugs for peptic ulcer and GERD** A02BB Prostaglandins A02BD Combinations for eradication of Helicobacter pylori A02ABX Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)
Medicinal product	Multiple
Product reference	NA
Procedure number	EMA/2017/09/PE

Marketing authorisation holder(s)	Multiple
Joint PASS	No
Research questions and objectives	The overall aim of this study is to evaluate the impact of the regulatory actions taken for ranitidine containing medicinal products following the 2019 referral procedure, using healthcare databases of six European countries.
Country(-ies) of study	the Netherlands, Spain, UK, Belgium, Germany and France
Author	Katia Verhamme, Peter Rijnbeek, Deborah Layton, Alexandra Pacurariu, Hanne van Ballegooijen

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1 List of Abbreviations

Abbreviation	Definition
API	Active Pharmaceutical Ingredient
CDM	Common Data Model
CHMP	Committee for Medicinal Products for Human Use
DDD	Defined Daily Dose
DHPC	Dear Healthcare Professional Communications
ECL	Enterochromaffin-like
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GERD	Gastro-esophageal reflux disease
H2	Histamine 2
H2RA	Histamine 2 Receptor Antagonists
ICH	International Conference on Harmonisation
IARC	International Agency for Research on Cancer
IMRD	IQVIA Medical Research Data
IPCI	Integrated Primary Care Information
LPD	Longitudinal Patient Database
NDMA	N-Nitrosodimethylamine
OMOP	Observational Medical Outcomes Partnership
OTC	Over The Counter
PDD	Prescribed Daily Dose
PRAC	Pharmacovigilance Risk Assessment Committee
SIDIAP	Information System for Research in Primary Care
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

2 Responsible Parties

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3 Abstract

Section	Description
Rationale and background	Ranitidine is a competitive and reversible inhibitor of the action of histamine and indicated for the management of peptic ulceration (with or without Helicobacter Pylori), Gastro-Esophageal Reflux Disease (GERD), reflux oesophagitis and Zollinger-Ellison syndrome. In 2019, results of a preliminary laboratory analysis have shown the presence of N-Nitrosodimethylamine (NDMA), a human carcinogen, in ranitidine. The European Commission triggered on 12 September 2019 a referral procedure to evaluate the relevance of these findings, the potential root causes and their impact on the benefit-risk balance of medicinal products containing ranitidine. Based on this evaluation, in April 2020 EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended the suspension of all ranitidine-containing medicines in the EU due to the presence of low levels of NDMA impurities. Many ranitidine-containing medicines have not been available in the EU for several months since the initiation of the referral, because national competent authorities have recalled them either due to levels of NDMA found in the products or as a precaution while the EMA review is ongoing. Healthcare professionals have been asked to advise patients on alternative medicines. In addition, in some Member States the outcome of the referral was communicated at national level through media campaigns, involving learned societies and medical associations to inform prescribing physicians and health care organisations about these changes. The unavailability of ranitidine-containing medicines is expected to cause patients to switch treatment to alternative medicines or alternative treatment strategies. The extent of switches to alternative medicines remains unknown as well as the rate of patients permanently discontinuing treatment following unavailability of ranitidine-containing medicines.
Research question and objectives	1. To determine **drug utilisation and prescription patterns** of medicinal products containing ranitidine (A02BA02) and alternative medicinal products (other H2 receptor antagonists, proton pump inhibitors and other medicinal products for acid-related disorders). Prescribing and utilisation of ranitidine and alternative medicinal products will be described as incident use and stratified by quarter, by referral period (pre-referral= September 2017- September 2019), in-referral = September 2019- March 2020, post-referral= April 2020–April 2022), by indication (GERD, gastric and duodenal ulcer (w/o H. Pylori), gastritis (w/o H. Pylori), duodenitis (w/o H. Pylori), Zollinger-Ellison syndrome, dyspepsia/indigestion) by age group, by sex, by formulation, and by country and data source.

	2. To describe **switching to alternative medicinal products**, covering the following product classes as a minimum: a. H2-receptor antagonists on class and substance level (as available in country of study conduct): ATC codesA02BA01 (cimetidine), A02BA03 (famotidine), A02BA04 (nizatidine), A02BA06 (roxatidine), A02BA08 (lafutidine), A02BA51 (cimetidine, combinations) and A02BA53 (famotidine, combinations) in patients using ranitidine during the pre-referral period (September 2017- September 2019) and switching to other H_2-receptor antagonists. b. medicinal products containing proton-pump inhibitors, on class and substance level (as available in country of study conduct): ATC codes A02BC01 (omeprazole), A02BC02 (pantoprazole), A02BC03 (lansoprazole), A02BC04 (rabeprazole), A02BC05 (esomeprazole), A02BC06 (dexlansoprazole) in patients using ranitidine during the pre-referral period and switching to other proton-pump inhibitors. c. other medicinal products for acid-related disorders classified by class level (5 digit) of the related ATC-Codes not included under 1.a. and 1.b. (e.g. use of antacids) in patients using ranitidine during the pre-referral period and switching to other substances. 3. To describe patients **permanently discontinuing** treatment with ranitidine-containing medicinal products without switching to alternative medicines: by quarter, by referral period (pre-referral, in-referral, post-referral), by prior ranitidine indication (including gastro-oesophageal reflux disease (GERD), gastric and duodenal ulcer (w/o H. Pylori), gastritis (w/o H. Pylori), duodenitis (w/o H. Pylori), Zollinger-Ellison syndrome and dyspepsia/indigestionby age group, by sex, by prior usage patterns of ranitidine (e.g. duration of use, dose) and by country and data source. 4. To **describe drug utilisation patterns in new starters of the therapy in the set of indications**, where ranitidine has been predominantly prescribed prior to suspension of ranitidine (e.g. GERD, peptic ulceration): prescribing and drug utilisation of medicinal products for treatment of the indication should be described by type of drug, by quarter, by referral period (pre-referral= September 2017-September 2019), in-referral = September 2019- March 2020, post-referral= April 2020–April 2022), age group, by sex, by formulation, and by country and data source
Research methods	
Study design	A retrospective population-based cohort study will be conducted using electronic health care records from six databases from six European countries.

Setting	Data will be extracted over a study period of 1st January 2017 until 1st January 2023 to cover the ranitidine pre and post referral periods
Variables	Demographics: age, sex Exposure of interest: Ranitidine and alternative to ranitidine (other H2RA, PPIs, antacids and other drugs used for peptic ulcer and GERD) Prescribing and utilisation of alternative medicinal products will be described by incident use by database, by calendar year, by quarter, by referral period (pre-referral= September 2017- September 2019, in-referral = September 2019 - March 2020, post-referral= April 2020 – April 2022), by age category, sex, by indication of use and by type of formulation. To present these data, we thus need information on not only information on demographics but also datasource, calendar year, type of formulation and indication of use.
Outcomes	Incidence of use of ranitidine and alternatives medicines to ranitidine (other H2RA, PPIs, antacids and other drugs used for peptic ulcer and GERD) Treatment discontinuation in patients treated with ranitidine Switching from ranitidine to alternative medicines
Data sources	Data from six databases from six European countries namely IPCI (the Netherlands), SIDIAP (Catalonia Spain) and IQVIA (UK IMRD, LPD Belgium, DA Germany and LPD France). Data from these databases have been mapped to the OMOP Common Data Model.
Data analysis	As this is a DUS study without a priori hypothesis, descriptive statistical analysis will be used providing counts, proportions and incidence rates. In particular the Incidence of ranitidine, discontinuation of ranitidine and switching from ranitidine to alternative drugs will be investigated. This will be explored by database, calendar year, by quarter, by referral period (pre-referral= September 2017- September 2019, in-referral = September 2019 - March 2020, post-referral= April 2020 – April 2022), by age category, sex, indication of use. The incident use of alternatives to ranitidine (other H2RA, PPIs, antacids and other drugs for peptic ulcer and GERD) will be described by quarter, by referral period and by calendar year. A Joinpoint regression model will be used to investigate changes in prescribing patterns over calendar time.
Plans for Disseminating and Communication	The final study report will be written in accordance with the GVP guidelines module VIII, (EMA/813938/2011) and information about this PASS will be entered into the publicly available EU PAS register before start of data analysis.

4 Amendments and Updates

Major and Minor Amendments

Major Amendments	Minor Amendments
• Not applicable	This is an amended version of the protocol where cumulative dose and use of H2RA for reason of hypersensitivity syndrome is removed from the protocol

Number	Date	Section of the Protocol	Amendment or update	Reason
1	16th September 2021	8.5.2: indication of use (and related sections in the protocol)	Use of H_2RA for reason of hypersensitivity is excluded	Not relevant in GP setting
2	16th September 2021	8.3 exposure of interest (and related sections in the protocol)	Cumulative dose of H_2RA and alternatives is removed	Not relevant for these research questions and to avoid crowding of the dataset

5 Milestones

Milestone	Planned date
Milestone	**Planned date**
Approval Study Protocol by EMA	TO BE COMPLETED
Registration in the EU PAS register	TO BE COMPLETED
Start of data collection	1st January 2017
End of data collection	1st January 2023
Final study report provided to EMA	28 February 2023
Manuscript to be provided to EMA	28 April 2023

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 H2-receptors on parietal cells in the stomach. It is indicated for the management of peptic ulceration (with or without Helicobacter Pylori), 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, gastritis/duodenitis (with or without H. Pylori) dyspepsia (acid indigestion), hyperacidity, and prevention of symptoms associated with consuming food and drink. Ranitidine is available for oral and parenteral administration. (1, 2) Ranitidine is available as prescription but also as over the counter drug indicated for the treatment of non-ulcer dyspepsia, indigestion, heartburn, and sour stomach.

In 2019, results of a preliminary laboratory analysis have shown the presence of N-Nitrosodimethylamine (NDMA), a human carcinogen, in ranitidine, a H_2-receptor antagonist. (3) 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.

In view of the above, the European Commission triggered on 12 September 2019 a referral procedure under Article 31 of Directive 2001/83/EC to evaluate the relevance of these findings, the potential root causes and their impact on the benefit-risk balance of medicinal products containing ranitidine. Based on this evaluation, in April 2020 EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended the suspension of all ranitidine-containing medicines in the EU due to the presence of low levels of NDMA impurities. (3) The CHMP noted that treatment alternatives for ranitidine are available.

Many ranitidine-containing medicines have not been available in the EU for several months since the initiation of the referral, because national competent authorities have recalled them either due to levels of NDMA found in the products or as a precaution while the EMA review is ongoing. Healthcare professionals have been asked to advise patients on alternative medicines.

In addition, in some Member States the outcome of the referral was communicated at national level through media campaigns, involving learned societies and medical associations to inform prescribing physicians and health care organisations about these changes.

The unavailability of ranitidine-containing medicines is expected to cause patients to switch treatment to alternative medicines or alternative treatment strategies. The extent of switches to alternative medicines

remains unknown as well as the rate of patients permanently discontinuing treatment following unavailability of ranitidine-containing medicines.

7 Research Questions and Objectives

The aim of this project is to evaluate the impact of these regulatory actions taken for ranitidine-containing medicinal products following the initiation of the 2019 referral procedure and to generate information about prescribing and use patterns of alternatives to ranitidine-containing medicines in patients previously treated with ranitidine, for patients permanently discontinuing ranitidine and for patients starting new treatment in the indications where ranitidine has been predominantly used prior to suspension (irrespective of whether receiving ranitidine previously or not).

The main objectives of this project are:

1. To determine ***drug utilisation and prescription patterns of medicinal products*** containing ranitidine (A02BA02) or alternative medicinal products. This will be described by incident use and stratified by:

- quarter
- referral period (pre-referral= September 2017- September 2019, in-referral = September 2019 - March 2020, post-referral= April 2020 – April 2022)
- indication of use: gastro-oesophageal reflux disease (GERD), gastric and duodenal ulcer (with or without (w/o) H. Pylori), gastritis (w/o) H. Pylori), duodenitis (w/o) H. Pylori), Zollinger-Ellison syndrome and dyspepsia/indigestion
- age group
- sex
- formulation
- country and data source.

2. To describe ***switching to alternative medicinal products***, covering the following product classes as a minimum:

   a. H2 receptor antagonists (H2RA) on class and substance level (as available in country of study conduct): ATC codesA02BA01 (cimetidine), A02BA03 (famotidine), A02BA04 (nizatidine), A02BA06 (roxatidine), A02BA08 (lafutidine), A02BA51 (cimetidine, combinations) and A02BA53

(famotidine, combinations) in patients using ranitidine during the pre-referral period and switching to other H2-receptor antagonists.

b. medicinal products containing proton-pump inhibitors (PPIs), on class and substance level (as available in country of study conduct): ATC codes A02BC01 (omeprazole), A02BC02 (pantoprazole), A02BC03 (lansoprazole), A02BC04 (rabeprazole), A02BC05 (esomeprazole), A02BC06 (dexlansoprazole) in patients using ranitidine during the pre-referral period and switching to other proton-pump inhibitors.

c. other medicinal products for acid-related disorders classified by class level (5 digit) of the related ATC-Codes not included under 1.a. and 1.b. (e.g. use of antacids) in patients using ranitidine during the pre-referral period and switching to other substances.

3. To describe patients permanently ***discontinuing treatment*** with ranitidine-containing medicinal products without switching to alternative medicines and stratify the analysis by: quarter, referral period (pre-referral, in-referral, post-referral), prior ranitidine indication (GERD, gastric and duodenal ulcer (w/o H. Pylori), gastritis (w/o H. Pylori), duodenitis (w/o H. Pylori), Zollinger-Ellison syndrome and dyspepsia/indigestion), age group, sex, prior usage patterns of ranitidine (e.g. duration of use, dose) and by country and data source.

4. To describe drug utilisation patterns in new starters of the therapy in the set of indications, where ranitidine has been predominantly prescribed prior to suspension of ranitidine (e.g. GERD, peptic ulceration, duodenitis (w/o H. Pylori), Zollinger-Ellison syndrome and dyspepsia/indigestion): ***prescribing and drug utilisation of medicinal products for treatment of the indication*** should be described by type of drug, by quarter, by referral period ((pre-referral= September 2017- September 2019, in-referral = September 2019 - March 2020, post-referral= April 2020 – April 2022), age group, by sex, by formulation, and by country and data source.

8 Research Methods

8.1 Study Design

A retrospective population-based cohort study will be conducted using electronic health care records from six databases from six European countries. This cohort will be used to conduct a drug utilization study with a time series analysis component to identify the potential impact of regulatory interventions taken for ranitidine-containing medicinal products following the initiation of the 2019 referral procedure.

8.2 Setting

This study will be conducted in six EU member state countries where ranitidine was marketed. Data from six databases from six European countries namely IPCI (the Netherlands), SIDIAP (Catalonia Spain) and IQVIA (UK IMRD, LPD Belgium, DA Germany and LPD France). Data of these databases have been mapped to the OMOP Common Data Model (see https://github.com/OHDSI/CommonDataModel/wiki for more details).(4)

8.2.1 Study Time Period

As this study should cover a time frame of 2 years prior to initiation of the referral (September 2017-September 2019) (pre-referral period), a time period of 2 years after initial CHMP recommendation for suspension which was April 2020 (April 2020–April 2022) (post-referral period), and the period between initiation and finalisation of the referral (in-referral period, September 2019 - March 2020), data will be extracted over a study period of 1st January 2017 until 1st January 2023, in order to cover the aforementioned pre and post referral periods, allowing for data lag and data refresh dates.

8.2.2 Follow-up Period and Censoring

For each patient, follow-up will start at the start of the study period or the date on which the patient enters the study population and contributes active follow-up time, whichever comes last (this defines index date). Follow-up will end at the end of the observation period or end of study period whichever comes first.

8.2.3 Study Population

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

8.2.4 Patient Selection

From the study population, we will identify (1) patients exposed to any of the drugs of interest (H2RA, PPI and other medicinal products for acid-related disorders)(see Annex 3. Appendix 1 – List of ATC codes). Cohorts will be constructed for patients exposed to each individual ingredient as well as to the respective drug class (H2RA (excluding ranitidine), PPI and antacids).

To describe the drug utilisation patterns of new starters of alternatives to ranitidine (research objective 4), we will also (2) define a cohort of patients diagnosed with conditions for which use of ranitidine was indicated prior to suspension (e.g. GERD, peptic ulcer disease (with or without H Pylori), Zollinger Ellison Syndrome

and dyspepsia/indigestion). This cohort will be defined according to the presence of relevant OMOP Condition Concepts (SNOMED-CT) and drug use.

8.2.4.1 Inclusion Criteria

The inclusion criteria are:

- All patients with an active registration status during the study time period. Active registration means that the patient is registered with the GP during the study period and thus contributing data to the study.
- Continuous enrolment in the database for more than 12 months

8.2.4.2 Exclusion Criteria

Patients will be excluded if they have missing age or sex. No other exclusion criteria will be applied.

8.3 Exposure

8.3.1 Exposures of interest

From the study population, a cohort will be defined based on patients exposed to any of the drugs of interest (Ranitidine, other H_2RA, PPI and other medicinal products for acid-related disorders).
Drug exposure in the CDM is standardised to RxNorm codes. 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 (Appendix 1). The Standardised Vocabularies also provide a map to ATC codes if this is of value. Cohorts will be constructed for patients exposed to each individual ingredient as well as to the respective drug class (H2 antihistamines (excluding ranitidine), PPI and antacids). The DRUG_EXPOSURE table contains the following relevant fields for this study:

8.3.2 Duration and cumulative 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:

Table 1 Drug exposure table

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 extraction transform load (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.

Next treatment episodes will be calculated which is the sum of the duration of the individual prescriptions/dispensings of the respective drug/treatment class of interest. A gap of more than 30 days between prescriptions, i.e., a gap of more than 30 days between the estimated end date of a drug and the start date of the same drug, will signal the end of the treatment episode.

The proportion of patients permanently discontinuing treatment with ranitidine needs to be provided by certain covariates including cumulative exposure of rantidine. This implies that – prior to ranitidine discontinuation - the cumulative duration of use – which is the sum of the duration of treatment episodes from study start until date of discontinuation needs to be calculated. [Data for each drug treatment episode

in particular start date and drug exposure end dates are pre-populated within the CDM enabling a consistent estimation of each treatment interval for each available data source] For analysis purposes, categories of cumulative duration of use defined by quartiles will be empirically based on the observed distribution of cumulative duration of use.

An example of the calculation of the cumulative duration prior to treatment discontinuation is described in figure 1. Patient A received 3 prescriptions for ranitidine resulting in a cumulative exposure duration of 150 days. As there is a gap of more than 90 days between the end date of the last ranitidine prescription and the end of the observation period, this patient is considered as discontinuing treatment in 2018 with a cumulative duration of 60 days in 2018. (see later for definition of treatment discontinuation)

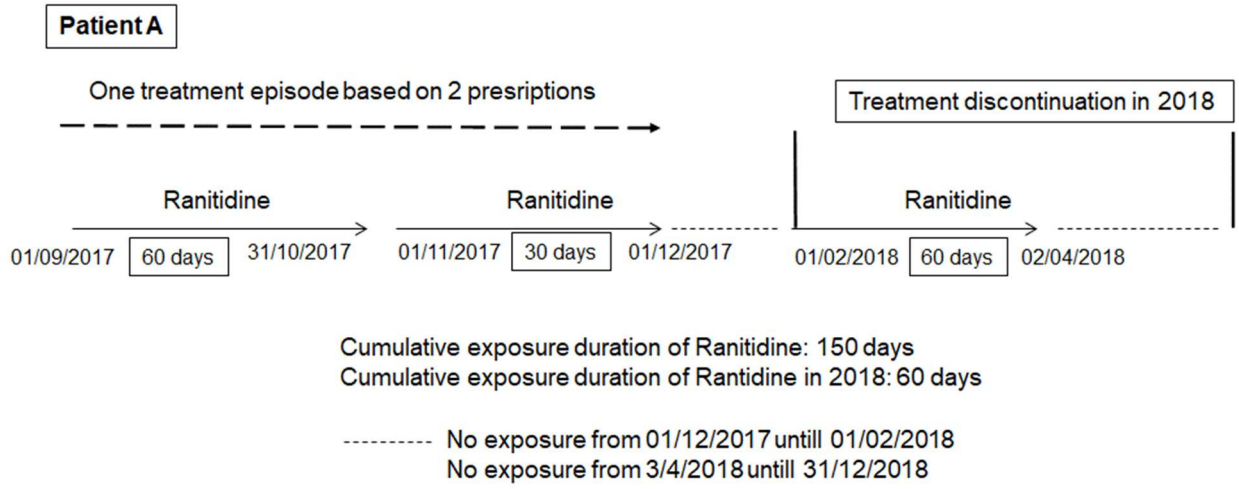

Figure 1: Calculation of cumulative duration

8.3.3 Dose in mg

Information on dose is needed for the description of patients discontinuing ranitidine treatment where the incidence of discontinuation is presented by ranitidine dose (i.e. prescribed daily dose (PDD)/defined daily dose ratio (DDD)) at start of observation period). (5)

If dosing instructions (= Sig) are available, the PDD will be the number of units per day multiplied by the strength. If dosing instruction is missing, the PDD can be derived from the quantity (e.g. number of pills prescribed/dispensed) multiplied by the strength and divided by the duration of a treatment episode. If information on dosing and strength is missing, the dose can be estimated using the Defined Daily Dose (DDD) as proxy.

An example of the calculation of the PDD/DDD is described in figure 2.

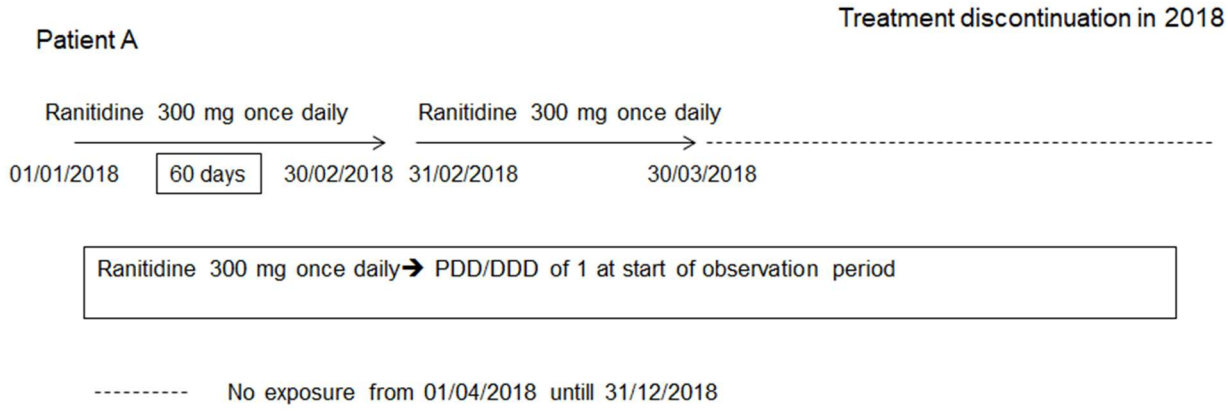

Figure 2: Calculation of PDD/DDD

8.4 Outcomes

8.4.1 Incident drug use

Drug utilization of ranitidine or alternative drugs will be presented as the number of new users per 1,000 persons. An incident user is defined as a patient with a record of exposure of interest and no exposure within the previous 365 days. For each database (and thus by country), stratum specific estimates will be presented separately according to: referral period (pre-referral= September 2017- September 2019, in-referral = September 2019 - March 2020, post-referral= April 2020 – April 2022), indication, age category, sex and formulation.

Incident drug use will be investigated (i) in the study population but as well in (ii) the cohort of patients diagnosed with conditions for which use of ranitidine was indicated prior to suspension of ranitidine.

To define the latter, we will define a cohort of patients diagnosed with conditions for which use of ranitidine was indicated prior to suspension (e.g. GERD, peptic ulcer disease (with or without H Pylori), Zollinger Ellison Syndrome, gastritis (with or without H Pylori), duodenitis (with or without H Pylori), dyspepsia/indigestion. This cohort will be defined according to the presence of relevant OMOP Condition Concepts (SNOMED-CT). Within this cohort, we will calculate the incidence of use of ranitidine as well as alternatives to ranitidine (other H_2RA, PPIs and acid suppressant medications) in the 180 days following the first diagnosis of any of the conditions of interest.

8.4.2 Discontinuation of ranitidine containing medicinal products

A patient will be defined as discontinuing ranitidine treatment in case there is a gap of more than 90 days between the end date of the last ranitidine episode and the end of the observation period. Patients with a gap of more than 90 days between ranitidine treatment episodes prior to the last ranitidine episode in the observation period are not considered as having discontinued treatment with ranitidine. If patients switch to alternative medicines this will not be considered as treatment discontinuation. These patients will be captured as individuals switching from ranitidine to alternative drugs. (see 8.4.3.)

Examples of treatment discontinuation are described in figure 3. If needed, a sensitivity analysis can be included in which the gap between the end of the last ranitidine episode and the end of the observation period is set at 60 or 30 days. Reducing this gap will be needed if we want to explore ranitidine discontinuation by quarter. For the main analysis, a gap of 90 days was chosen in line with common definitions to define “treatment discontinuation” for chronic therapy. (6, 7)

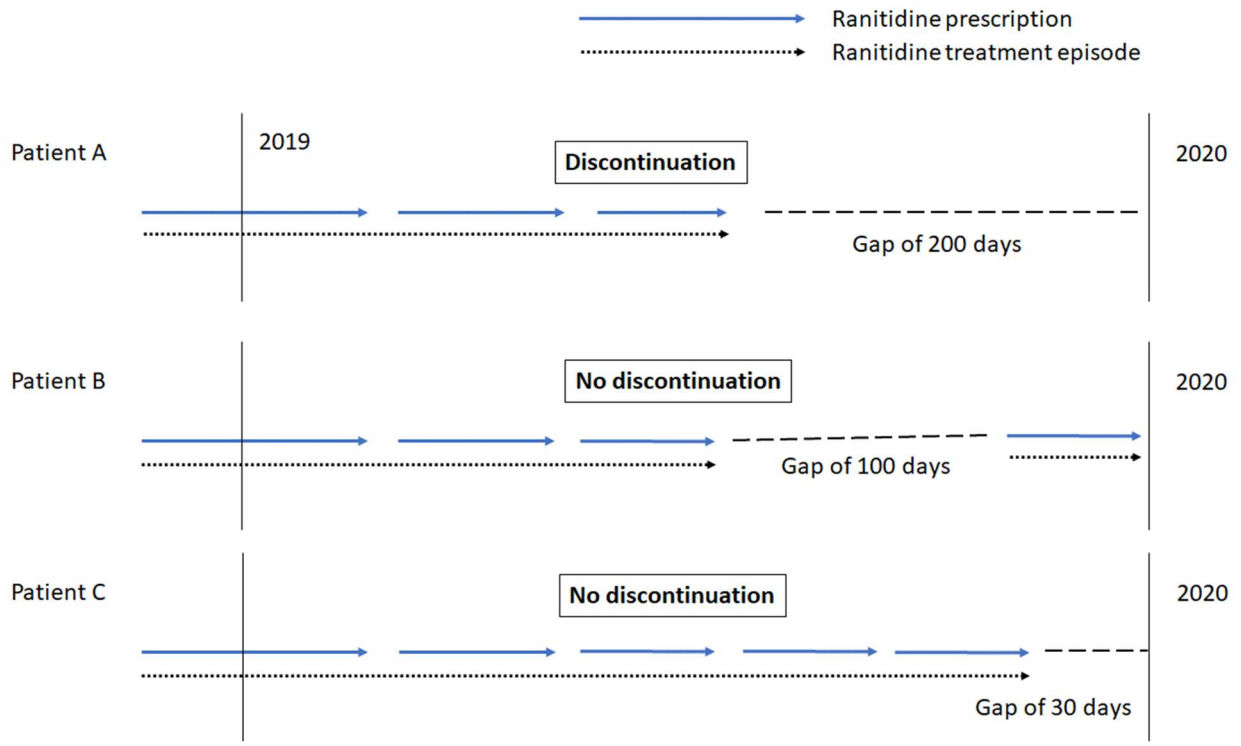

Figure 3. Examples of ranitidine discontinuation

Patient A represents a treatment discontinuation as more than 90 days between end date of last treatment episode and end of the observation period. Patient B does not represent ranitidine treatment discontinuation as less than 90 days between last ranitidine treatment episode and end of observation period although there is a gap of more than 90 days between the third and fourth ranitidine treatment episode. Patient C also does not represent treatment discontinuation as less than 90 days between the end date of the last treatment episode and the end of the observation period.

For estimation of the discontinuation of ranitidine per calendar interval, the numerator will consist of the number of ranitidine users per interval identified *and having discontinued treatment.* The denominator will consist of all ranitidine users in that specific interval. As we will observe multiple observation periods (e.g. pre, inter and post referral), this implies that an individual can be flagged as discontinuing ranitidine treatment on multiple occasions during the study period.

In addition, a sensitivity analysis will be conducted investigating the incidence of patients *permanently discontinuing treatment with ranitidine* (thus only identifying patients who discontinued treatment and did not restart in subsequent observation periods).

8.4.3 Switching from ranitidine to other alternative medicines (H2RA, PPI or other medicinal products for acid-related disorders)

Switching will be categorized as:

1) *switchers within a period of current exposure of ranitidine*

switching from ranitidine to alternative medicines in case there is an overlap of at least 1 day between the end date of the ranitidine treatment episode and the start date of the first prescription of the alternative medicine. Concomitant use of antibiotics for the treatment of H. Pylori (amoxicilline, clarithromycine, tetracycline, metronidazole, azithromycin, levofloxacine) will never fulfil the definition of switching. Also overlap of more than 15 days of use of ranitidine with use of alternative medicines will not be considered as treatment switch. Overlap is most likely to occur for use of ranitidine in combination with other medicinal products for acid-related disorders.

Switching to ranitidine will also be considered in case there is a gap of maximum 90 days between the end date of the ranitidine treatment episode and the start of the alternative drugs. Examples of switching from ranitidine use to alternative drugs (H_2RA, PPI or other medicinal products for acid-related disorders) are described in figure 4.

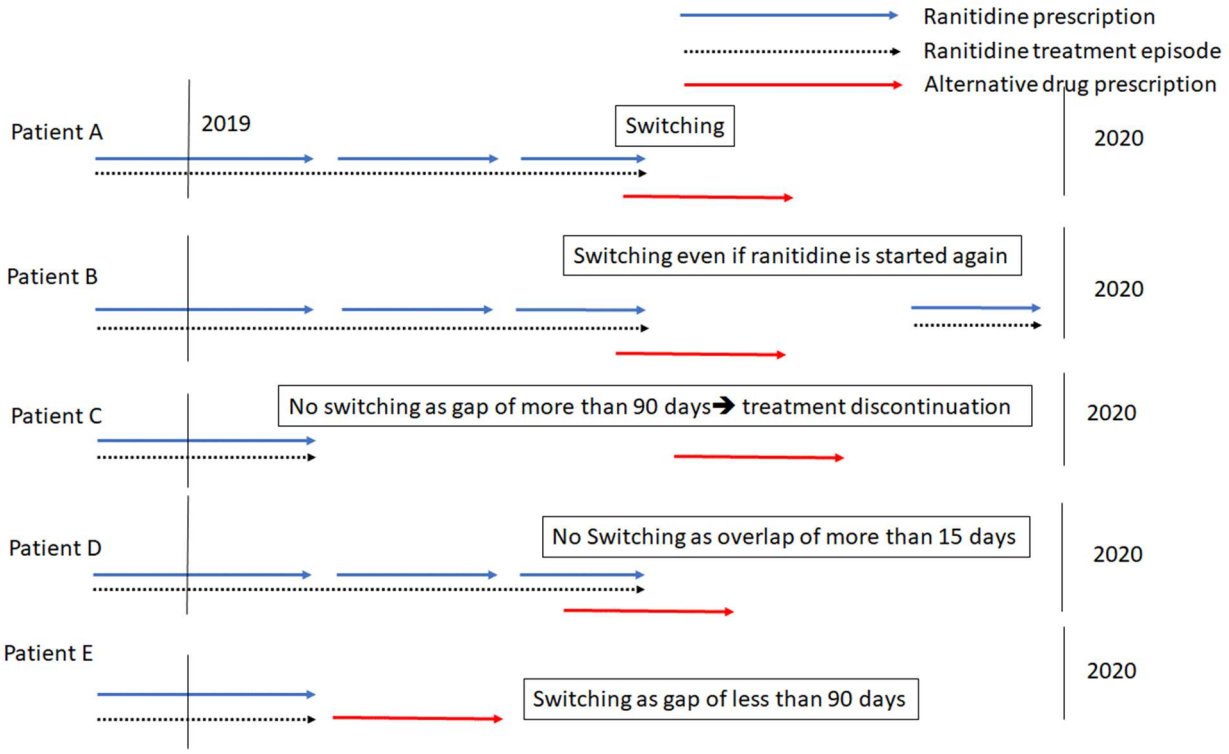

Figure 4. Examples of early switching from ranitidine to alternative treatments

Patient A represents a switcher as overlap between the ranitidine and alternative medicines prescription. Patient B represents a switcher as overlap between the ranitidine treatment episode and alternative medicines prescription even if ranitidine is initiated later again. Patient C does not represent an early switcher as more than 90 days between the end of the ranitidine treatment episode and the start of alternative treatment. Patient D is not a switcher as overlap between ranitidine and alternative drugs of more than 15 days. Patient E represents switching as less than 90 days between the end of the ranitidine treatment episode and the start of alternative treatment.

2) *late switching* from ranitidine to alternative medicines (H_2RA, PPI or other medicinal products for acid-related disorders) following interrupted use of ranitidine.

In real life, ranitidine is not necessarily taken continuously, and treatment use is characterised by episodes of continuous use, interrupted when symptoms abate and re-initiation of treatment when symptoms get worse again.

If patients with interrupted treatment of ranitidine need to switch to alternative medicines, a substantial number would not fulfil the criteria of switching (as defined above) as the gap between treatment episodes of ranitidine to start of alternative medicines might be more than 90 days.

As this would underestimate the proportion of switchers, we have now also defined *"late switching to alternative drugs following interrupted use of ranitidine".* 'Late switching' of ranitidine treatment can only apply to patients that did not fulfil the criterium of early switching (see 1/ *switchers within a period of current exposure of ranitidine)*. A late switcher will be defined as a patient switching from treatment episodes of ranitidine to a treatment episode of alternative treatments but with a gap of more than 90 days between the end of the ranitidine treatment episode and the start of alternative treatment. The maximum gap between the end of the ranitidine treatment episode and the start of the alternative treatment can be maximum 1 year (365 days) (Figure 5). To explore whether extending this gap influences the number of late switching, a sensitivity analysis will be conducted where the maximum gap is increased to 2 years (730 days).

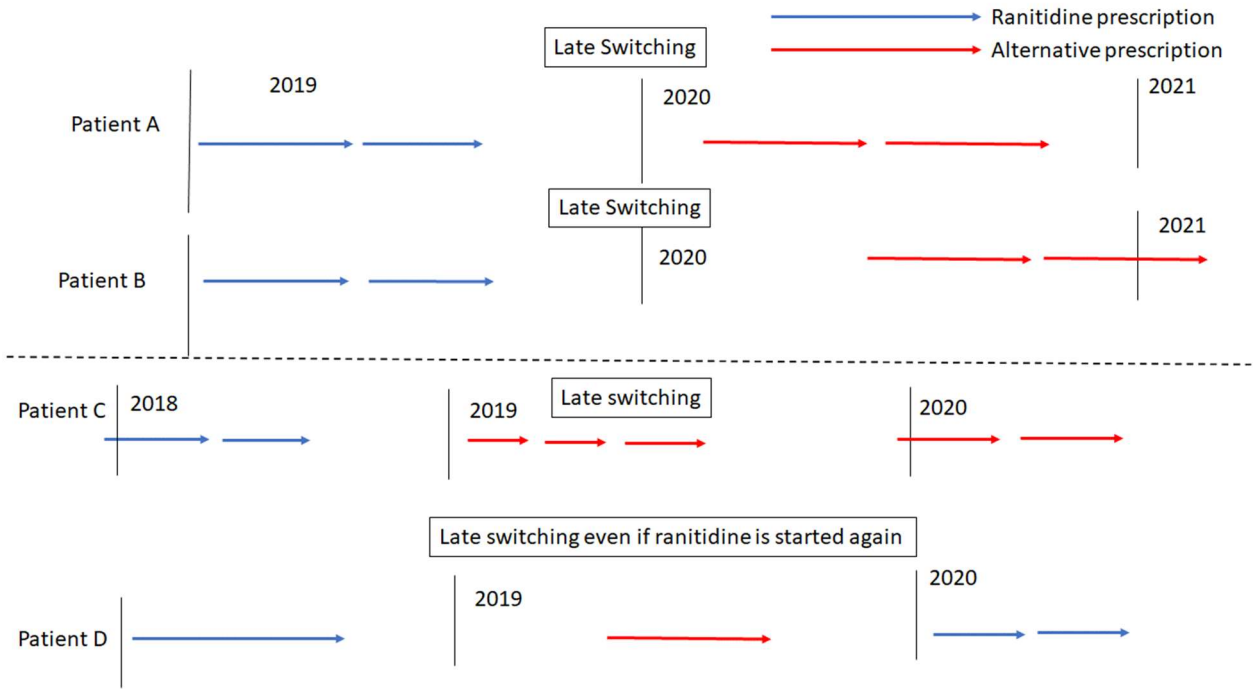

Figure 5: Examples of late switching from ranitidine to alternative treatments

For the estimation of the incidence of switching per calendar interval, the numerator will consist of the number of ranitidine users in each interval identified as being a switcher. These patients will therefore be a sub-cohort of ranitidine users. The denominator will consist of all patients defined as ranitidine users. As we will observe multiple observation periods (e.g. pre, inter and post referral), this implies that an individual can be flagged as a switcher on multiple occasions during the study period.

In general, switching will be presented (for the switching within a period of current use as well as for late switching) by three mutually exclusive categories in particular:

- Switching to other H2 receptor antagonist
- Switching to PPI (no switching to other H2 receptor antagonist)
- Switching to other treatment such as antacids (no switching to PPI or other H2 receptor antagonist)

8.5 Variables

In order to meet the study objectives, the following parameters will be obtained from the selected data sources and analysed:

- Demographics
- Indication of use
- Clinical characteristics at time of treatment initiation

8.5.1 Demographics

Sex will be regarded as a fixed covariate throughout the study period.

Age will be assessed at the start of each calendar year. For paediatric use, additional age cut-offs will be used namely the ICH paediatric age categories (small children (<2 years); children (2 to 11 years); adolescents (12 to 18 years). Also, to provide insight in the use of ranitidine in the elderly, apart from 10-year age categories, age will in addition be categorized into <18 years, 18<75 years and ≥ 75 years.

8.5.2 Indication of use

All indications of use of interest will be defined according to relevant OMOP Condition Concepts (SNOMED-CT) prior to the first prescription of ranitidine or alternatives to ranitidine (i.e. other H2RA, PPI and other medicinal products for acid-related disorders) during study follow-up. (4)

The indication of use will be assessed both in the past 6 months (180 days)(main analysis) and in the past 12 months (365 days)(sensitivity analysis) of the first prescription of ranitidine or alternative drugs during the study period. Based on the results from the drug utilisation study on Ranitidine and other histamine-H_2-receptor antagonists (EMA/2017/09/PE) we know that using a look-back of 365 days did not increase the patients with “indication of use” with more than 25% and for this reason we assume that using a look back of 180 days will be regarded the main method.

The indication of use for ranitidine treatment or alternative medicinal products will be defined according to presence of clinical diagnoses associated with gastro-oesophageal reflux disease (GERD), gastric and duodenal ulcer (w/o H. Pylori), gastritis (w/o H. Pylori), duodenitis (w/o H. Pylori), Zollinger-Ellison syndrome and dyspepsia/indigestion. . Dyspepsia/indigestion will only be considered as indication in the absence of a more specific diagnosis.

Whether a condition coincides with an infection of H Pylori is either derived from the SNOMED CT describing presence of H. Pylori (see annex 4) or will be derived from the clinical diagnosis of interest in combination with RxNorm concept IDs for use of antibiotics in combination with a prescription for use of ranitidine or alternative drugs.

The OMOP Condition Concepts related to the indications of interest are listed in Appendix 2.

8.5.3 Clinical characteristics at time of treatment initiation

In the previous paragraph, we have defined which indications of use that we are going to investigate. However, as ranitidine (and alternative medicines) might be used for other (off-label) indications, we will explore the type of conditions and procedures within a window of 14 days prior to the index date using Systematized Nomenclature of Medicine (SNOMED CT) codes with all descendent codes included. The frequency of conditions reported in the 14 days prior to treatment initiation will be reported in exploratory tables. This will give us insight in potential indications of use for ranitidine (and alternative drugs) which might be further explored as (off-line) indication of use based on the frequency of occurring.

8.6 Data Sources

For this study, we will include Electronic Health Record data from six primary care databases throughout Europe, specifically IPCI (the Netherlands), SIDIAP (Spain), IMRD (UK), LPD (Belgium), DA Germany and LPD France. All of these databases have their data mapped to the OMOP CDM. Characteristics of these databases with regard to the total number of individuals and database update are described in Table 2:

Table 2 Characteristics of databases

Database	Managing Organisation	Country	Individuals*	History
LPD Belgium	IQVIA	Belgium	1.1 M	2005 - present
LPD France	IQVIA	France	18.1M	1994 - present
DA Germany	IQVIA	Germany	37.3 M	1992 - present
UK IMRD	IQVIA	UK	15.2M	2005- Q2 2020*
IPCI	Erasmus MC	Netherlands	2.6M	1996 - present
SIDIAP	IDIAP Jordi Gol	Spain	7.9M	2006 - present

**Updated data will be available soon – does not only consist of individuals with active follow-up (also historical patients)*

Integrated Primary Care Information (IPCI), The Netherlands (Erasmus)

IPCI is collected from EHR records of patients registered with their GPs throughout the Netherlands. (8) The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996. (8)The median follow-up is 2.6

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. 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. (8) The IPCI database is currently increasing the update frequency because of the COVID-19 pandemic (now updated till September 2020 for a large selection of GP practices).

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

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff. (9) The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M 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. 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.

IQVIA Medical Research Data (IMRD) UK (IQVIA)

IMRD UK is a large database of anonymised electronic medical records collected at Primary Care clinics throughout the UK. (10) 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. All protocols must be submitted to an independent Scientific Review Committee prior to study conduct.

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 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers a time period from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation 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. (11) Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) 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% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 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. No registration or approval is required for drug utilisation studies.

Longitudinal Patient Database (LPD) France (IQVIA)

LPD France is a computerised network of physicians including GPs who contribute to a centralised database of anonymised patient EMR. (12) Currently, >1200 GPs from 400 practices are contributing to the database covering 18.1M patients in France. The database covers a time period from 1994 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

8.7 Sample Size

This study is a characterisation of all patient data captured in the data assets and meeting inclusion criteria for exposure to ranitidine. 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 3 describes the number of users of ranitidine and other H2 receptor antagonists based on the numbers from the previous EMA tender project - EMA/2017/09/PE – Ranitidine and other histamine-H2-receptor antagonists – drug utilisation study. These numbers will change based on new available data.

Table 3. Number of patients per H2 receptor antagonist based on data from 1992 to 2019*

	RAnitidine	cimetidine	famotidine	nizatidine	roxatidine
IPCI	61,063	2,364	704	71	-
SIDIAP	94,962	275	2,092	-	-
Belgium LPD	52,683	642	-	-	-
France LPD	31,613	4,989	658	84	-
Germany DA	150,513	13,063	13,254	3,010	1,122
UK IMRD	615,485	99,287	2,257	35,234	-
Total	1,006,319	120,620	18,965	35,690	1,122

*might change based on new available data

8.8 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.

8.8.1 CDM 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 (13) 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 6-7 below on a simulated dataset.

DATA QUALITY ASSESSMENT

SYNTHEA SYNTHETIC HEALTH DATABASE

Results generated at 2019-08-22 14:15:06 in 29 mins

	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 6: Summary overview of the Data Quality Dashboard

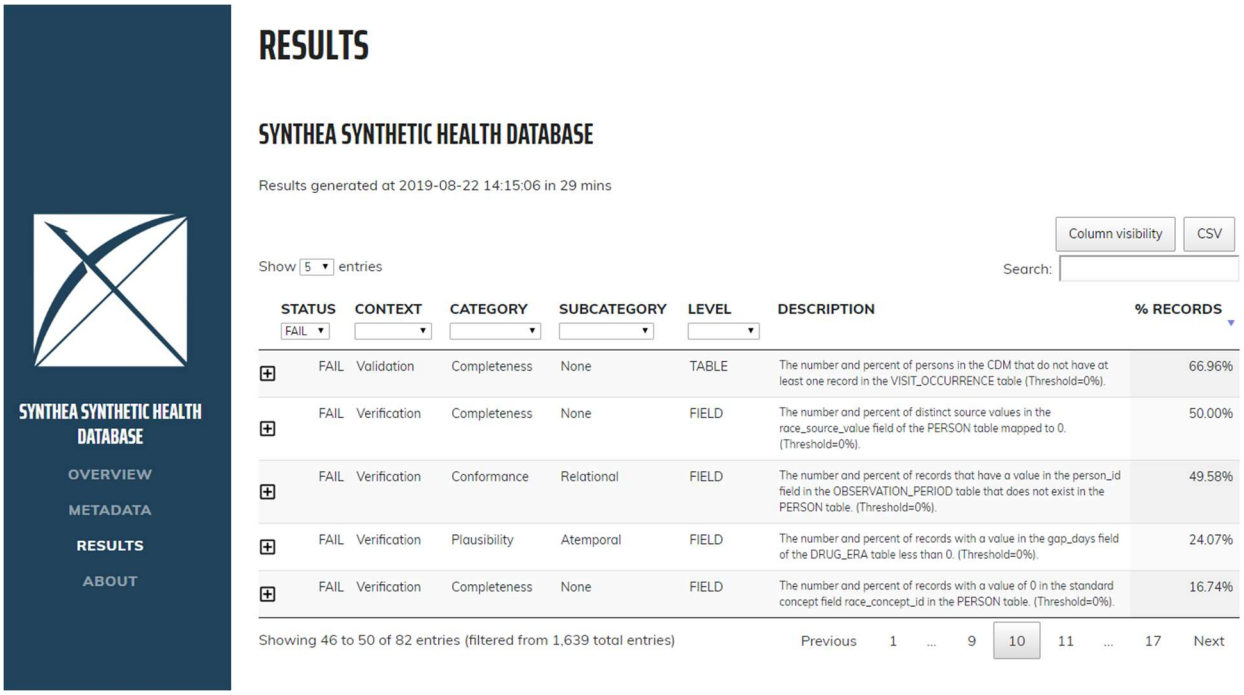

Figure 7: Detailed result view of the Data Quality Dashboard

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.

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. (5) 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 H2RA 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.

8.9 Data Analysis

8.9.1 General considerations

Continuous variables will be described using mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be described by the number and percentage of patients in each category. The number of patients with missing data for key variables will be reported- no imputation will be performed to handle missing data. Confidence intervals (CIs) of 95% will be presented for means using a normal approximation. All results will be presented separately by database and pooled over the different databases if appropriate and feasible. To prevent the identification of individuals, cells containing low frequency counts of (1-5) will be suppressed.
Mock tables are presented in Annex 5.

8.9.2 Descriptive analyses

8.9.2.1 Cohort characteristics

An initial exploratory analysis will be conducted for each country-specific cohort to summarise baseline demographic characteristics, medical conditions at time of treatment initiation, indication and exposure.

8.9.2.2 Incidence of drug use (ranitidine or alternative drugs)

An incident user is defined as a patient with a record of exposure of interest and no exposure within the previous 365 days. Incident drug use will be expressed as the number of users per 1,000 persons per quarter, calendar year and by referral period. For each database (and thus by country), stratum specific estimates will be presented separately according to: referral period (pre-, during- and post-referral), indication, age category, sex and formulation.

The pre-referral period will consist of the period from September 2017-September 2019

The in-referral period will consist of September 2019-March 2020

The post-referral period consists of the period between April 2020-April 2022.

Incident drug use will be provided for ranitidine, other H_2RA (class and substance level), PPI and other medicinal products for acid-related disorders.

8.9.2.3 Incidence of Ranitidine Discontinuation

Discontinuation will be expressed as the number of patients identified as discontinuing (within an observation period as well as permanently discontinuing – see definition of treatment discontinuation) ranitidine treatment per 1,000 ranitidine users presented per quarter and calendar year. For each database (and thus by country), stratum specific estimates will be presented separately according to: referral period (pre-referral= September 2017- September 2019, in-referral = September 2019 - March 2020, post-referral= April 2020 – April 2022), indication of use, by age categories, sex, formulation and usage patterns of ranitidine (duration of use, dose). With regard to the latter, the incidence of discontinuation will be described per quartile of cumulative duration of use. With regard to the dose, the proportion of discontinuation will be provided for previous ranitidine use at a dose of <1 PDD/DDD, 1 PDD/DDD or >1 PDD/DDD at start of ranitidine initiation. To present the results by cumulative duration of use , categories of use will be created based on quartiles.

8.9.2.4 Incidence of switching from Ranitidine to alternative medicines

Switching onto alternative medications other than ranitidine will be expressed as the number of patients identified as switching treatment per 1,000 ranitidine users per quarter and per calendar year. For each database (and thus by country), stratum specific estimates will be presented separately according to: referral period (pre-referral= September 2017- September 2019, in-referral = September 2019 - March 2020, post-referral= April 2020 – April 2022), indication, by age category, sex, formulation and usage patterns of ranitidine (duration of use, dose). Not only the total number of switching will be provided but also the type of switching (i.e. from ranitidine to the type of alternative medicine) and results will be visualized by means of a Sankey or a Sunburst plot.

8.9.2.5 Drug utilisation patterns in new starters of alternatives to ranitidine

To describe the drug utilisation patterns of new starters of alternatives to ranitidine, we will also define a cohort of patients diagnosed with conditions for which use of ranitidine was indicated prior to suspension (e.g. GERD, peptic ulcer disease (with or without H Pylori), Zollinger Ellison Syndrome, dyspepsia/indigestion. This cohort will be defined according to the presence of relevant OMOP Condition Concepts (SNOMED-CT). Within this cohort, we will calculate the incidence of use of ranitidine as well as alternatives to ranitidine (other H2RA, PPIs and acid suppressant medications). For estimation of the incidence drug use in the 180 days following the first diagnosis of interest, the numerator will consist of the number of incident users in this interval. The denominator will consist of the number of patients with the indication of use and contributing at least one day of follow-up time in the 180 days following the first diagnosis of interest. Incidence rates will be described by database further stratified by referral period, age, sex and formulation.

8.9.2.6 Time-series analysis of changes in prescribing patterns following the regulatory intervention

A Joinpoint regression model will be used to investigate changes in prescribing patterns of ranitidine over calendar time (as recommended by Annex 2 of ENCePP Methodological Guide. Joinpoint regression calculates time points of trend line changes and offer an alternative if the date of the intervention is unknown or if there are multiple intervention points.(14)

The response variable will be the incidence proportion of ranitidine (by calendar year and by quarter), and the independent variable will be calendar year 2017 to 2023 (by quarter). The joinpoint regression model will be fitted as follows: The number of patients receiving a prescription of ranitidine in each quarter as the numerator, the number of individuals present in the database by quarter (denominator) as an “offset term”, and the quarter as the regressor variable. The minimum number of joinpoints specified will be zero, the maximum number of joinpoints will equate to the total number of regulatory interventions and major milestones of the referral regulatory procedures. For this study this means that the timepoints of intervention for ranitidine prescribing will be September 2019 (start of referral period), April 2020 (recommendation of suspension) and September 2020 (Confirmation of suspension). The predicted moments of change in trend will then compared with the known times of regulatory interventions in each country bearing in mind that there might be earlier timepoints relevant for trend changes as in some member states ranitidine prescribing

may have started to decline earlier. Analysis will start with zero joinpoints, and test whether ≥1 joinpoints improves the model (based on a 5% significance level).

8.9.3 Sensitivity analysis

Table 4: Sensitivity analyses

Main Definition	Alternative Definition
Indication of use	• 365 days prior to treatment initiation
Ranitidine discontinuation	• A sensitivity analysis will be included in which the gap between the end of the last ranitidine prescription and the end of the observation period is set at 60 or 30 days (instead of 90 days)
Ranitidine discontinuation	• In addition, a sensitivity analysis will be conducted investigating the proportion of patients permanently discontinuing treatment with ranitidine (thus no re-use of ranitidine with subsequent discontinuation in subsequent observation periods).
Ranitidine late switching	• A sensitivity analysis will be conducted where the maximum gap between the end of the ranitidine treatment episode and the start of the alternative treatment is increased to 2 years (730 days)

8.10 Quality Control

IQVIA Quality Management System (QMS)

As the coordinating centre for this collaboration, the IQVIA QMS will be applied. This IQVIA QMS is built upon the quality and regulatory compliance principles established by the standards and guidelines from the International Standards Organisation (ISO) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The QMS encompasses all matters that individually or collectively influence the quality and regulatory compliance of the offerings in scope, and defines systems, processes and tools that enable the proposal to meet the appropriate quality standards and Good clinical practice compliance requirements. IQVIA has implemented an effective support network to ensure that the QMS is embedded across all projects.

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IQVIA Quality Management System (QMS) and in accordance to the appropriate global procedure.

EMC Quality Management System (QMS)

This project will be executed setting a high-quality standard with regard to i) protocol development, ii) data-extraction as well as data-analysis and iii) clear, fast and unbiased dissemination (via study report and manuscript). EMC, in partnership with IQVIA follows the following standards to ensure that the study is conducted in the most efficient way

All participating databases are registered on the EMA's ENCePP resources database. This implies that research is conducted according to the ENCePP Code of Conduct and the Guidelines on Good Pharmacovigilance Practices. Accordingly, the research protocol will be submitted to the EU-PAS register and the final study report will be uploaded and available for consultation in the ENCePP registry.

For this study, we will use data mapped to the OMOP Common Data Model. OHDSI and EHDEN have developed multiple quality control mechanisms for the Common Data Model. These are described in high detail in the recent Chapter 15 of The Book of OHDSI (http://book.ohdsi.org/DataQuality.html). This includes a large number of plausibility, conformance, and completeness checks for all the data domains.

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, proper source code management, and full code documentation.

The analytical pipeline of this study will be made available in opensource for full transparency and replicability.

8.11 Limitations of the Research Methods

As we use data from electronic health care records, data is not pro-actively collected for specific research questions implying that we might miss certain covariates of interest. Related to this, conditions which determine the indication of the use of ranitidine and alternatives to ranitidine might be underreported in the source databases.

Second, as low dose ranitidine, other H2RA, PPIs and antacids are also available over the counter, there is the potential of underreporting of use of these drugs. Also, as primary care databases are proposed, the use of ranitidine and alternatives to ranitidine in the hospital setting is lacking.

.

Third, a balanced representation of all EU healthcare services and settings cannot be provided but it is anticipated that the total amount of included patients and users will provide valuable insights of the use of ranitidine (and alternatives to ranitidine) in Europe.

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

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.

9.1 Required submissions and approvals in the study target countries

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. IQVIA follow best practice guidelines for the conduct of pharmacoepidemiologcal studies. (27)

10 Management and Reporting of Adverse Events/ Adverse Reactions

This study will adhere to the International Society for Pharmacoepidemiology (ISPE) good pharmacoepidemiology practice guidelines. This is a non-interventional study design, which is based on secondary data use. Expedited reporting of Adverse Events (AE) and Adverse Drug Reactions (ADR) is not required.

11 Plans for Disseminating and Communicating Study Results

11.1 Final Analyses and reporting

The final study report will be written in accordance with the GVP guidelines module VIII, (EMA/813938/2011). (15) In accordance with the 2010 EU pharmacovigilance legislation (Articles 10 or 10a of Regulation (EC) No 726/2004; Articles 21a or 22a of Directive 2001/83/EC), information about this PASS will be entered into the publicly available EU PAS register before the start of data collection. Updates to the

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

study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

11.2 Publications

Study findings will be considered for publication as open access. Any publication will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE). (16) Reporting will be consistent with the RECORD-PE guidelines for reporting of studies conducted using observational routinely collected health data.(17)

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Annexes

Annex 1. List of stand-alone documents

NA

Annex 2. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Study of exposure and use patterns of alternatives to ranitidine-containing medicines in patients treated with ranitidine

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	8.2.1
1.1.2 End of data collection[3]	☒	☐	☐	8.2.1
1.1.3 Progress report(s)	☒	☐	☐	5.Milestones
1.1.4 Interim report(s)	☐	☐	☒	

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5.Milestones
1.1.6 Final report of study results.	☒	☐	☐	5.Milestones

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.Background and rationale
2.1.2 The objective(s) of the study?	☒	☐	☐	7. research objectives
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.3 Study population
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1 Study Design
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.6 Data sources
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.4 outcomes of interest
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2.3 Study population
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.2.1 study time period
4.2.2 Age and sex	☒	☐	☒	
4.2.3 Country of origin	☒	☐	☐	8.2 setting
4.2.4 Disease/indication	☒	☐	☐	8.2.4 Patient Selection
4.2.5 Duration of follow-up	☒	☐	☐	8.2.2 Follow-up
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.3 study population and 8.2.4 patient selection

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3 Exposure
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	8.3.2 cumulative duration
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.3.3 dose in mg
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.2.4 patient selection

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.11 limitations
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.11 limitations
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.11 limitations

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	Stratified analysis are done for effect modifiers of interest (age, gender, calendar year, cumulative duration and indication of use)

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.6 Data sources
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6 Data sources
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.6 Data sources
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.6 Data sources
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6 Data sources
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6 Data sources
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6 Data sources
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6 Data sources
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.6 Data sources

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.9 Data-analysis
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.7 Sample size

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are descriptive analyses included?	☒	☐	☐	8.9 Data-analysis
10.4 Are stratified analyses included?	☒	☐	☐	8.9 Data-analysis
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.9 Data-analysis
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	8.9 Data-analysis
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.9 Data-analysis
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.9 Data-analysis

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.8 data management
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8 data management
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	Review by EMA

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias?	☒	☐	☐	8.11 limitations

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.2 Information bias?	☒	☐	☐	8.11 limitations
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.11 limitations
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.7 Sample size

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9. Protection of human subjects
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9. Protection of human subjects

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4 Amendment and updates

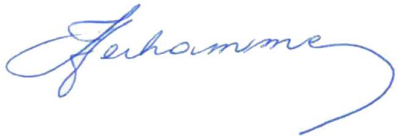
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11. plan for Disseminating and communicating of study results
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11. plan for Disseminating and communicating of study results

Comments:

Name of the main author of the protocol: Katia Verhamme

Date: 16th September 2021

Signature: 

Annex 3. – List of ATC codes

ATC code	Description
H_2 Receptor Antagonists	
A02BA01	Cimetidine
A02BA02	Ranitidine
A02BA03	Famotidine
A02BA04	Nizatidine
A02BA05	Niperotidine
A02BA06	Roxatidine
A02BA08	Lafutidine
A02BA51	Cimetidine combinations
A02BA53	Famotidine combinations

ATC code	Description
PPI	
A02BC01	Omeprazole
A02BC02	Pantoprazole
A02BC03	Lansoprazole
A02BC04	Rabeprazole
A02BC05	Esomeprazole
A02BC06	Dexlansoprazole
A02BC07	Dexrabeprazole
A02BC08	Vonoprazan
A02BC53	Lansoprazole, combinations

ATC code	Description
Antacids	
A02AAs	Magnesium compounds
A02AB	Aluminium compounds
A02AC	Calcium compounds
A02AD	Combinations and complexes of aluminium, calcium and magnesium compounds
A02AF	Antacids with antiflatulents
A02AG	Antacids with antispasmodics
A02AH	Antacids with sodium bicarbonate
A02AX	Antacids, other combinations

ATC code	Description
Other drugs for peptic ulcer and GERD	
A02BB	Prostaglandins
A02BD	Combinations for eradication of Helicobacter pylori
A02BX	Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)

ATC code	Description
Use of antibiotics for eradication of H Pylori	
Amoxicillin	J01CA04
Clarithromycin	J01FA09
Tetracyline	J01AA07
Azithromycin	J01FA10
Metronidazole	P01AB01
Levofloxacine	J01MA12

Annex 4 - Concept Sets

Below the concept sets are presented that are used in the study for the indications of drug use. 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	With H Pylori
4265600	Gastric ulcer	397825006	No
45763550	Antral ulcer	4911000119101	No
4248429	Gastric ulcer without hemorrhage AND without perforation	73481001	No
36716880	Gastric ulcer caused by chemical	723105009	No
4080599	Gastrocolic ulcer	24060004	No
4341234	Gastric erosion	235651006	No
44808499	Gastric ulcer with obstruction	849591000000103	No
4197099	Combined gastric AND duodenal ulcer	79806007	No
4319441	Acute gastric ulcer	95529005	No
4049466	Gastric ulcer with hemorrhage	15902003	No
37017373	Gastric ulcer caused by drug	713638002	No
4027942	Esophagogastric ulcer	10699001	No
42572805	Erosion of gizzard	341851000009107	No
4059178	Gastrojejunal ulcer	16121001	No
37119136	Ulcer of stomach due to lymphocytic gastritis	724521003	No

concept_id	concept_name	concept_code	With H Pylori
42538546	Infection causing ulcer of stomach	762274007	No
45757242	Erosive gastritis	1086791000119100	No
37110307	Ulcer of stomach due to eosinophilic gastritis	724520002	No
4197598	Multiple gastric ulcers	313425006	No
36716879	Gastric ulcer caused by ionizing radiation	723104008	No
4340787	Healed gastric ulcer	235702004	No
4331322	Prepyloric ulcer	22620000	No
4189591	Pyloric ulcer	39204006	No
36717606	Gastric ulcer caused by fungus	723101000	No
4318534	Chronic gastric ulcer	95530000	No
36716877	Gastric ulcer due to parasitic infection	723102007	No
36713527	Gastric ulcer due to Zollinger-Ellison syndrome	717891008	No
4321586	Gastric ulcer with perforation	9829001	No
36716876	Gastric ulcer caused by virus	723100004	No
36716875	Gastric ulcer caused by bacterium	723099007	No
195851	Gastric ulcer without hemorrhage, without perforation AND without obstruction	59913009	No
4028243	Chronic gastrojejunal ulcer	128288009	No
4266523	Gastric ulcer with hemorrhage AND perforation	62366003	No
44791257	Non-steroidal anti-inflammatory drug induced gastric ulcer	248891000000103	No
4211001	Chronic gastric ulcer with hemorrhage	57246001	No
4057953	Acute gastric ulcer with perforation	19850005	No
4057076	Healed gastric ulcer leaving a scar	196775009	No
4223226	Gastric ulcer with perforation but without obstruction	84038009	No
4195231	Acute gastric ulcer without hemorrhage AND without perforation	67964002	No
4101104	Gastrojejunal ulcer without hemorrhage AND without perforation	2783007	No
36716878	Gastric ulcer caused by alcohol	723103002	No
4342642	Chronic drug-induced ulcer of stomach	235650007	No
4341233	Acute drug-induced ulcer of stomach	235648004	No
44808503	Gastrojejunal ulcer with obstruction	849621000000100	No
4087594	Acute gastric mucosal erosion	18665000	No
4341235	Multiple gastric erosions	235652004	No
45757062	Gastric ulcer due to Helicobacter pylori	103691000119106	Yes
4188456	Stress ulcer of stomach	415624002	No
4076267	Gastro-esophageal reflux disease with ulceration	245754007	No
198190	Gastric ulcer with perforation AND obstruction	72486001	No
45757397	Gastric ulcer caused by non-steroidal anti-inflammatory drug in therapeutic use	129141000119104	No
4025501	Acute gastric ulcer with obstruction	196632005	No
4102254	Gastroesophageal erosion	301007008	No
4150681	Chronic gastric ulcer with perforation	31301004	No
4231580	Acute gastric ulcer with hemorrhage	89748001	No
40481540	Acute erosive gastritis	444926003	No
764846	Gastric ulcer caused by cytomegalovirus	689991000119100	No
4041707	Gastric ulcer with hemorrhage but without obstruction	16694003	No
4055895	Chronic gastric ulcer with obstruction	196639001	No

concept_id	concept_name	concept_code	With H Pylori
4296611	Chronic gastric ulcer without hemorrhage AND without perforation	76796008	No
4024984	Acute gastrojejunal ulcer	196707000	No
4271442	Chronic erosive gastritis	63137003	No
37110309	Anastomotic ulcer of stomach caused by drug	724523000	No
4006992	Acute gastric erosion associated with drug ingestion	111350000	No
4143871	Bleeding gastric erosion	307233002	No
4310838	Gastric ulcer induced by anti-platelet agent	424301005	No
4222477	Gastrojejunal ulcer with hemorrhage	84124004	No
196443	Gastric ulcer without hemorrhage AND without perforation but with obstruction	31452001	No
4232767	Helicobacter-associated pyloric ulcer	89662003	Yes
4207217	Gastric ulcer with hemorrhage AND obstruction	53877005	No
4147351	Gastrojejunal ulcer with perforation	30183003	No
4179773	Gastrojejunal ulcer with hemorrhage but without obstruction	50663005	No
37110308	Anastomotic ulcer of stomach caused by Helicobacter pylori	724522005	Yes
433515	Chronic gastrojejunal ulcer with hemorrhage	62838000	No
4024985	Acute gastrojejunal ulcer with obstruction	196712004	No
4273874	Gastrojejunal ulcer with hemorrhage AND perforation	64094003	No
4169592	Acute gastric ulcer with hemorrhage AND perforation	48974009	No
4001167	Acute ulcerative gastroenteritis complicating pneumonia	109814008	No
4101870	Chronic gastrojejunal ulcer with perforation	2807004	No
438188	Gastrojejunal ulcer without hemorrhage AND without perforation but with obstruction	47152002	No
197914	Chronic gastric ulcer with perforation but without obstruction	36246001	No
4177387	Chronic gastrojejunal ulcer without hemorrhage AND without perforation	4269005	No
4205670	Bleeding stress ulcer of stomach	308882008	No
195583	Chronic gastric ulcer without hemorrhage AND without perforation but with obstruction	60531007	No
438795	Chronic gastrojejunal ulcer without hemorrhage, without perforation AND without obstruction	41626001	No
4294973	Chronic gastric ulcer with hemorrhage AND with perforation	76181002	No
42538071	Cushing ulcer of stomach	738791006	No
4024986	Chronic gastrojejunal ulcer with obstruction	196719008	No
4147683	Acute gastrojejunal ulcer without hemorrhage AND without perforation	30514008	No
4274491	Acute gastrojejunal ulcer with hemorrhage	63954007	No
199062	Acute gastric ulcer without hemorrhage, without perforation AND without obstruction	54053008	No
192954	Acute gastric ulcer without hemorrhage AND without perforation but with obstruction	81225008	No
193795	Acute gastric ulcer with hemorrhage but without obstruction	70418001	No

concept_id	concept_name	concept_code	With H Pylori
200769	Chronic gastric ulcer without hemorrhage, without perforation AND without obstruction	1567007	No
197018	Chronic gastric ulcer with hemorrhage but without obstruction	76078009	No
4038489	Gastrojejunal ulcer with perforation but without obstruction	11818002	No
200137	Acute gastric ulcer with perforation AND obstruction	43694004	No
4069766	Gastrojejunal ulcer with perforation AND obstruction	21759003	No
4071203	Gastric ulcer with hemorrhage AND perforation but without obstruction	2066005	No
4280942	Acute gastrojejunal ulcer with perforation	66636001	No
36683388	Curling's ulcer of stomach	781203005	No
4069838	Gastric ulcer with hemorrhage, with perforation AND with obstruction	17593008	No
198467	Acute gastric ulcer with hemorrhage AND obstruction	46708007	No
201885	Chronic gastric ulcer with hemorrhage AND with obstruction	85859006	No
4175673	Gastrojejunal ulcer with hemorrhage AND obstruction	42698006	No
37110306	Gastric ulcer caused by Helicobacter pylori and non-steroidal anti-inflammatory agent	724519008	Yes
194680	Acute gastric ulcer with perforation but without obstruction	90628007	No
4206315	Chronic gastric ulcer with perforation AND with obstruction	55483002	No
439858	Gastrojejunal ulcer without hemorrhage, without perforation AND without obstruction	35517004	No
4244406	Chronic gastrojejunal ulcer with hemorrhage but without perforation	59356009	No
437598	Acute gastrojejunal ulcer with perforation but without obstruction	72395008	No
195845	Acute gastric ulcer with hemorrhage, with perforation AND with obstruction	53337006	No
4183005	Gastrojejunal ulcer with hemorrhage, with perforation AND with obstruction	54798007	No
432951	Acute gastrojejunal ulcer without hemorrhage AND without perforation but with obstruction	10389003	No
4217947	Acute gastrojejunal ulcer with hemorrhage AND perforation	81387001	No
436729	Chronic gastrojejunal ulcer with hemorrhage AND obstruction	90257004	No
196442	Chronic gastric ulcer with hemorrhage AND with perforation but without obstruction	74341002	No
4164920	Chronic gastrojejunal ulcer with hemorrhage AND perforation	45640006	No
436460	Acute gastrojejunal ulcer without hemorrhage, without perforation AND without obstruction	77987006	No
198801	Chronic gastric ulcer with hemorrhage, with perforation AND with obstruction	85787009	No

concept_id	concept_name	concept_code	With H Pylori
435579	Chronic gastrojejunal ulcer with perforation but without obstruction	62477005	No
434400	Chronic gastrojejunal ulcer without hemorrhage AND without perforation but with obstruction	56579005	No
4336971	Gastrojejunal ulcer with hemorrhage AND with perforation but without obstruction	87796008	No
441063	Acute gastrojejunal ulcer with hemorrhage AND obstruction	72408002	No
444102	Chronic gastrojejunal ulcer with perforation AND with obstruction	10897002	No
199855	Acute gastric ulcer with hemorrhage AND with perforation but without obstruction	17067009	No
438468	Acute gastrojejunal ulcer with hemorrhage but without obstruction	59515005	No
435846	Acute gastrojejunal ulcer with perforation AND obstruction	72219001	No
441328	Acute gastrojejunal ulcer with hemorrhage AND with perforation but without obstruction	66673003	No
442314	Acute gastrojejunal ulcer with hemorrhage, with perforation AND with obstruction	58711008	No
443779	Chronic gastrojejunal ulcer with hemorrhage, with perforation AND with obstruction	24001002	No
437326	Chronic gastrojejunal ulcer with hemorrhage AND with perforation but without obstruction	46523000	No

Table A4: Concept set for Duodenal Ulcer

concept_id	concept_name	concept_code	With H Pylori
4198381	Ulcer of duodenum	51868009	No
4194177	Familial hypergastrinemic duodenal ulcer	6761005	No
4105935	Duodenal ulcer with increased serum pepsinogen I	29755007	No
4024842	Recurrent duodenal ulcer	196671008	No
42538548	Ulcer of duodenum due to infection	762276009	No
44808500	Duodenal ulcer with obstruction	8496010000000109	No
4209746	Duodenal ulcer without hemorrhage AND without perforation	56776001	No
4340230	Duodenal erosion	235692002	No
4296319	Normopepsinogenemic familial duodenal ulcer	76338009	No
4285720	Giant duodenal ulcer	68834009	No
4099014	Duodenal ulcer with hemorrhage	27281001	No
37203820	Tremor, nystagmus, duodenal ulcer syndrome	782935003	No
4299937	Postpyloric ulcer	78054007	No
37110319	Duodenal ulcer caused by fungus	724534002	No
4229614	Duodenal ulcer with perforation	88968005	No
37117196	Duodenal ulcer caused by ionizing radiation	724531005	No
4028242	Chronic duodenal ulcer	128286008	No
4182589	Childhood duodenal ulcer	43035002	No
36717645	Duodenal ulcer due to Zollinger-Ellison syndrome	717892001	No
37110315	Duodenal ulcer caused by drug	724529001	No
4057053	Acute duodenal ulcer	196652006	No
36713516	Eosinophilic duodenal ulcer	717878007	No
4197099	Combined gastric AND duodenal ulcer	79806007	No

concept_id	concept_name	concept_code	With H Pylori
37110317	Ulcer of duodenum caused by chemical	724532003	No
37110318	Duodenal ulcer caused by virus	724533008	No
36713517	Lymphocytic duodenal ulcer	717879004	No
37117176	Duodenal ulcer caused by bacterium	723884008	No
4040644	Familial duodenal ulcer associated with rapid gastric emptying	16516008	No
4149010	Duodenal ulcer with hemorrhage but without obstruction	35560008	No
4342649	Stress ulcer of duodenum	235688009	No
4174560	Duodenal ulcer induced by anti-platelet agent	423643000	No
4265479	Acute duodenal ulcer with perforation	61347001	No
4138962	Acute duodenal ulcer without hemorrhage AND without perforation	32490005	No
4084844	Duodenal ulcer with hemorrhage AND obstruction	18367003	No
36716253	Duodenal ulcer caused by non-steroidal anti-inflammatory drug	722200003	No
435305	Duodenal ulcer without hemorrhage AND without perforation but with obstruction	18169007	No
4315039	Duodenal ulcer with perforation but without obstruction	86983005	No
4027729	Acute duodenal ulcer with hemorrhage	12847006	No
4298227	Duodenal ulcer with perforation AND obstruction	77410006	No
438469	Duodenal ulcer without hemorrhage, without perforation AND without obstruction	34580000	No
4173408	Chronic duodenal ulcer with perforation	49916007	No
4222896	Chronic duodenal ulcer without hemorrhage AND without perforation	40214005	No
4214461	Acute erosion of duodenum	39344002	No
4024840	Acute duodenal ulcer with obstruction	196658005	No
436453	Chronic duodenal ulcer with obstruction	196666001	No
37110314	Duodenal ulcer caused by Helicobacter pylori	724528009	Yes
4232181	Chronic duodenal ulcer with hemorrhage	89469000	No
4031954	Duodenal ulcer with hemorrhage AND perforation	23812009	No
436148	Chronic duodenal ulcer with hemorrhage but without obstruction	62341002	No
437323	Chronic duodenal ulcer with hemorrhage AND obstruction	34021006	No
432354	Chronic duodenal ulcer with perforation but without obstruction	34602004	No
443770	Chronic duodenal ulcer without hemorrhage AND without perforation but with obstruction	28082003	No
441062	Acute duodenal ulcer with hemorrhage AND obstruction	87756006	No
4336230	Acute duodenal ulcer with hemorrhage AND perforation	86895006	No
435578	Acute duodenal ulcer with perforation but without obstruction	22511002	No
4341240	Cushing ulcer of duodenum	235689001	No
435859	Acute duodenal ulcer without hemorrhage AND without perforation but with obstruction	75342000	No

concept_id	concept_name	concept_code	With H Pylori
440755	Acute duodenal ulcer without hemorrhage, without perforation AND without obstruction	23693000	No
434402	Acute duodenal ulcer with hemorrhage but without obstruction	66767006	No
433246	Chronic duodenal ulcer without hemorrhage, without perforation AND without obstruction	57940000	No
4035167	Duodenal ulcer with hemorrhage AND with perforation but without obstruction	15115006	No
4049270	Duodenal ulcer with hemorrhage, with perforation AND with obstruction	12355008	No
439058	Chronic duodenal ulcer with perforation AND obstruction	60551006	No
4289830	Chronic duodenal ulcer with hemorrhage AND perforation	36975000	No
37110316	Duodenal ulcer caused by Helicobacter pylori and non-steroidal anti-inflammatory agent	724530006	Yes
4342650	Curling's ulcer of duodenum	235690005	No
434070	Acute duodenal ulcer with perforation AND obstruction	62936002	No
437021	Acute duodenal ulcer with hemorrhage, with perforation AND with obstruction	41986000	No
440756	Chronic duodenal ulcer with hemorrhage, with perforation AND with obstruction	86258000	No
438796	Chronic duodenal ulcer with hemorrhage AND with perforation but without obstruction	81142005	No
435855	Acute duodenal ulcer with hemorrhage AND with perforation but without obstruction	51847008	No

Table A5: Concept set for gastritis/duodenitis

Concept ID	Concept Name	Concept Code	With H Pylori
192667	Atrophic gastritis	84568007	No
193249	Acute hemorrhagic gastritis	2367005	No
195300	Alcoholic gastritis	2043009	No
195306	Gastroduodenitis	196731005	No
195309	Eosinophilic gastritis	66329006	No
199866	Acute gastritis	25458004	No
201059	Hypertrophic gastritis	60002000	No
201340	Gastritis	4556007	No
3655344	Gastritis caused by Strongyloides stercoralis	860887000	No
3655346	Gastritis caused by Cryptosporidium	860889002	No
4025859	Radiation gastritis	197012004	No
4035787	Atrophic nonerosive nonspecific gastritis	15445004	No
4056512	Allergic gastritis	1824008	No

4057236	Dietetic gastritis	197028009	No
4057513	Chronic superficial gastritis	196735001	No
4057514	Corrosive gastritis	196740009	No
4112288	Viral gastritis	285344007	No
4140520	Atrophic-hyperplastic gastritis	3308008	No
4141636	Acute adolescent mastitis	266580009	No
4148707	Superficial nonerosive nonspecific gastritis	35223008	No
4172870	Gastritis of newborn	276527006	No
4175028	Irritant gastritis	42541005	No
4175610	Nonerosive nonspecific gastritis	50874004	No
4175960	Phlegmonous gastritis	49781004	No
4178492	Atrophic fundic gland gastritis	42740008	No
4179473	Gastritis medicamentosa	52305004	No
4179507	Cytomegaloviral gastritis	429300008	No
4198048	Hypertrophic glandular gastritis	80018001	No
4221118	Staphylococcal mastitis	8287004	No
4225273	Chronic gastritis	8493009	No
4232467	Chronic antral gastritis	89790007	No
4232623	Helicobacter-associated gastritis	89538001	Yes
4233621	Arcanobacterial mastitis	405818003	No
4235552	Corynebacterial mastitis	408639009	No
4236238	Lymphocytic gastritis	360375007	No
4238211	Reflux gastritis	57433008	No
4245117	Acute and chronic gastritis	396337009	No
4247651	Bile-induced gastritis	72950008	No
4250891	Emphysematous gastritis	7399006	No
4253032	Postgastrectomy gastritis	7475005	No
4253355	Toxic gastritis	74361008	No
4271442	Chronic erosive gastritis	63137003	No
4292402	Caustic injury gastritis	37693008	No
4318962	Superficial gastritis	22304002	No
4337545	Gastric polyposis	87252009	No
4340125	Uremic gastritis	235659008	No
4340673	Infective gastritis	235655002	No
4340674	Reactive gastritis	235656001	No
4340675	Sepsis-related gastritis	235657005	No
4340676	Chronic follicular gastritis	235660003	No
4340677	Chronic cystic gastritis	235661004	No
4340776	Chronic granulomatous gastritis	235662006	No
4341236	Acute neutrophilic gastritis	235654003	No
4341237	Isolated granulomatous gastritis	235663001	No
4342643	Crohn's disease of stomach	235664007	No

36684448	Gastritis with upper gastrointestinal hemorrhage	9,7801E+13	No
36713501	Metaplastic gastritis	717861003	No
36714965	Cystic fibrosis with gastritis and megaloblastic anemia syndrome	720401009	No
36716872	Gastritis caused by bacterium	723096000	No
36716873	Gastritis caused by fungus	723097009	No
36716874	Parasitic infection causing gastritis	723098004	No
37110305	Acute superficial gastritis	724517005	No
37110307	Ulcer of stomach due to eosinophilic gastritis	724520002	No
37119136	Ulcer of stomach due to lymphocytic gastritis	724521003	No
37312136	Mast cell gastritis	789697006	No
40481540	Acute erosive gastritis	444926003	No
44784282	Chronic antral gastritis with hemorrhage	698352000	No
45757242	Erosive gastritis	1,08679E+15	No
45757570	Gastric hemorrhage due to idiopathic erosive gastritis	2,18541E+14	No
45757783	Gastric hemorrhage due to alcoholic gastritis	4,0241E+13	No
45768629	Gastric hemorrhage due to erosive gastritis	7,071E+12	No
45769496	Helicobacter pylori-associated gastritis	708164002	Yes
45769497	Helicobacter heilmannii gastritis	708165001	Yes
45772107	Suppurative gastritis	2,1871E+13	No
46269819	Gastric hemorrhage due to allergic gastritis	1,08263E+15	No
46269837	Gastric hemorrhage due to chronic superficial gastritis	1,08512E+15	No
46269911	Gastric hemorrhage due to hypertrophic gastritis	1,08716E+15	No
46269912	Gastric hemorrhage due to irritant gastritis	1,08781E+15	No
46269935	Gastric hemorrhage due to pyloric gastritis	1,09036E+15	No
46269953	Gastric hemorrhage due to viral gastritis	1,09294E+15	No
46270025	Gastric hemorrhage due to eosinophilic gastritis	1,23411E+14	No
46270145	Gastric hemorrhage due to atrophic gastritis	1,50721E+14	No
46270959	Gastritis cystica profunda	708964003	No
46273027	Collagenous gastritis	711499009	No
195306	Gastroduodenitis	196731005	No
433516	Duodenitis	72007001	No
437027	Hemorrhagic duodenitis	95531001	No
3663212	Duodenitis caused by Ancylostoma	840503000	No
3663213	Duodenitis caused by Cytomegalovirus	840504006	No
4210469	Crohn's disease of duodenum	56287005	No
4340231	Chronic duodenitis	235693007	No
4341241	Tuberculous duodenitis	235694001	No
36713511	Allergic duodenitis	717872008	No
36713512	Eosinophilic duodenitis	717873003	No
36713513	Infective duodenitis	717875005	No
36713515	Granulomatous duodenitis	717877002	No

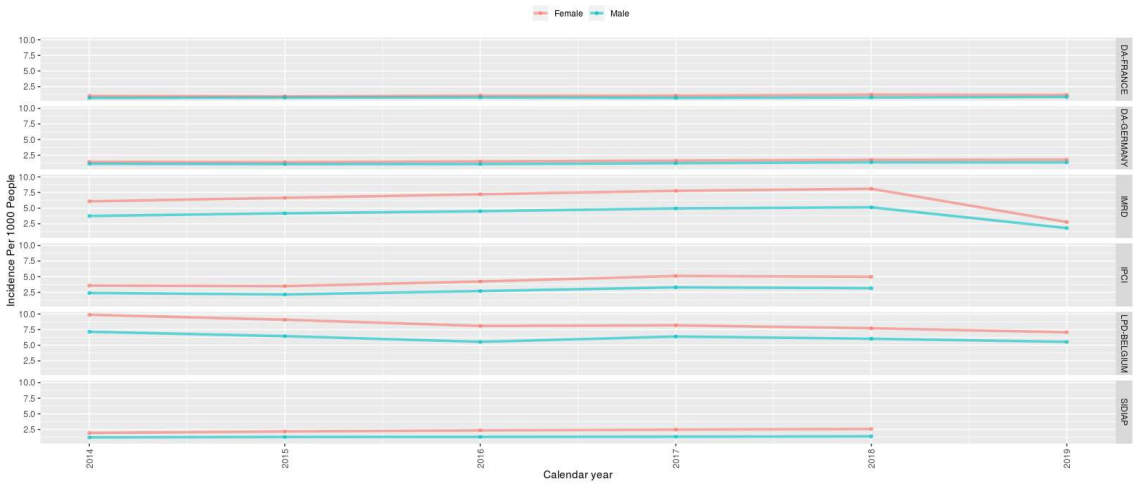
36717643	Lymphocytic duodenitis	717874009	No
37109932	Duodenitis caused by ingestible alcohol	723882007	No
37109933	Duodenitis caused by ionizing radiation	723883002	No
37110311	Duodenitis caused by Helicobacter pylori	724525007	Yes
37110312	Duodenitis caused by drug	724526008	No
37110313	Duodenitis caused by chemical	724527004	No
37116439	Duodenitis caused by Tropheryma whipplei	733148009	No
37396135	Acute duodenitis	715834004	No

Table A5: Concept set for Dyspepsia/Indigestion

concept_id	concept_name	concept_code
439418	Indigestion	162031009
4091959	Flatulent dyspepsia	249511005
4100532	Psychogenic dyspepsia	191972002
4114304	Drug-induced dyspepsia	299969005
4168182	Under care of dyspepsia specialist nurse	416202003
4221768	Discharged from care of dyspepsia specialist nurse	417691002
4289526	Nonulcer dyspepsia	3696007
40317098	Hyperacidity	155722007
40346375	Dyspepsia/indigestion NOS	266505001
40399049	Dyspepsia	196752002
40640558	Dyspepsia	87548005
44790450	Undiagnosed dyspepsia	203661000000105
439418	Indigestion	162031009
4012218	No indigestion	162028008
4012493	Indigestion symptom NOS	162035000
4091515	Indigestion NOS	249510006
4174390	Vagus indigestion	42567000
4212516	Mild dietary indigestion	331987008
40304416	Indigestion symptoms	139295001
40304420	Indigestion	139299007
40304426	Indigestion symptom NOS	139303002
40317098	Hyperacidity	155722007
40325737	Gastric irritation	162027003

Annex 5 – Mock figures and tables

Mock Figures



Mock Figure 1: Incidence of Ranitidine by calendar year (stratified by sex)

Incidence will as well be presented by quarter and in the pre-referral, referral and post-referral period.

These figures will also be generated for alternative drugs (other H2RA, PPIs, antacids and other drugs for peptic ulcer and GERD)

Mock tables

Table 1: Incidence of ranitidine and alternative medicines. (by class and by individual drugs) – Expressed as number of users per 1,000 persons

	LPD France							DA Germany		
	2017	2018	2019	2020	2021	2022	2023	2017	2018	2019 etc
H2 receptor antagonist										
Ranitidine										
Cimetidine										
Famotidine										
Nizatidine										
Roxatidine										
PPI										
Omeprazole										
Pantoprazole										
Lansoprazole										
Rabeprazole										
Esomeprazole										
Dexlansoprazole										
Dexrabeprazole										
Vonoprazan										
Lansoprazole, combinations										
Antacids										
Magnesium compounds										
Aluminium compounds										
Calcium compounds										

	LPD France							DA Germany		
	2017	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2017**	**2018**	**2019 etc**
Combinations and complexes of aluminium, calcium and magnesium compounds										
Antacids with antiflatulents										
Antacids with antispasmodics										
Antacids with sodium bicarbonate										
Antacids, other combinations										
Other drugs for peptic ulcer and GERD										
Prostaglandins										
Combinations for eradication of Helicobacter pylori										
Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)										

Table 2: Incidence of alternative medicines (expressed as number of users per 1,000 persons) by strata of interest

	H2RA	Cimetidine	Famotidine	Nizatidine	Roxatidine	PPI	Omeprazole	Pantoprazole…*.
Pre-referral								
In-referral								
Post-referral								
Indication of use: - GERD - Peptic ulcer - Peptic Ulcer with H Pylori								

	H2RA	Cimetidine	Famotidine	Nizatidine	Roxatidine	PPI	Omeprazole	Pantoprazole…*.
- Gastritis/duodenitis - Gastritis/duodenitis with H Pylori - Zollinger Ellison Syndrome - Dyspepsia/Indigestion								
Age group: <2 years 2-11 years 12-18 years <=10 years								

	H2RA	Cimetidine	Famotidine	Nizatidine	Roxatidine	PPI	Omeprazole	Pantoprazole…*.
>10-<=20 years >20-<=30 years >30-<=40 years >40-<=50years >50-<=60 years >60-<=70 years >70-<=80 years >80-<=90 years >90 <18 years 18<75 years								

	H2RA	Cimetidine	Famotidine	Nizatidine	Roxatidine	PPI	Omeprazole	Pantoprazole…*.
≥ 75 years								
Sex: Female Male								
Formulation Oral Parenteral								

This table will be generated for all alternatives for ranitidine (other H2RA, PPIs, antacids and other drugs for peptic ulcer and GERD) (at class level and by substance level). The results by calendar year is provided in table 1. The results by quarter (by calendar year) will be provided by means of a figure.

Table 3: Switching (expressed as number of switchers per 1,000 persons) from current exposure of ranitidine to alternative medicinal products

	LPD France							DA Germany		
	2017	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2017**	**2018**	**2019 etc**
Number of ranitidine users switching to alternative drugs										
Total number of ranitidine users										
Frequency of switchers										
Number of ranitidine users switching to alternative drugs										
Switching to*:										
Cimetidine										
Famotidine										
Nizatidine										
Roxatidine										
PPI										
Omeprazole										
Pantoprazole										
Lansoprazole										
Rabeprazole										
Esomeprazole										
Dexlansoprazole										
Dexrabeprazole										

	LPD France							DA Germany		
	2017	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2017**	**2018**	**2019 etc**
Vonoprazan										
Lansoprazole, combinations										
Antacids										
Magnesium compounds										
Aluminium compounds										
Calcium compounds										
Combinations and complexes of aluminium, calcium and magnesium compounds										
Antacids with antiflatulents										
Antacids with antispasmodics										
Antacids with sodium bicarbonate										
Antacids, other combinations										
Other drugs for peptic ulcer and GERD										
Prostaglandins										
Combinations for eradication of Helicobacter pylori										
Other drugs for peptic ulcer and gastro-										

	LPD France							DA Germany		
	2017	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2017**	**2018**	**2019 etc**
oesophageal reflux disease (GORD)										

*"Switching to" will be expressed as proportion of total number of ranitidine switchers. As an example, if the number of Ranitidine switchers in 2017 (For LPD France) is 3500 and 3000 of these switch to omeprazole, the percentage of switching attributed by omeprazole will be 86%

Table 4: Late switching (expressed as number of switchers per 1,000 persons) to alternative medicinal products

	LPD France							DA Germany		
	2017	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2017**	**2018**	**2019 etc**
Number of ranitidine users switching to alternative drugs										
Total number of ranitidine users										
Frequency of switchers										
Number of ranitidine users switching to alternative drugs										
Switching to*:										
Cimetidine										
Famotidine										
Nizatidine										
Roxatidine										
PPI										
Omeprazole										
Pantoprazole										
Lansoprazole										
Rabeprazole										
Esomeprazole										
Dexlansoprazole										
Dexrabeprazole										

	LPD France							DA Germany		
	2017	2018	2019	2020	2021	2022	2023	2017	2018	2019 etc
Vonoprazan										
Lansoprazole, combinations										
Antacids										
Magnesium compounds										
Aluminium compounds										
Calcium compounds										
Combinations and complexes of aluminium, calcium and magnesium compounds										
Antacids with antiflatulents										
Antacids with antispasmodics										
Antacids with sodium bicarbonate										
Antacids, other combinations										
Other drugs for peptic ulcer and GERD										
Prostaglandins										
Combinations for eradication of Helicobacter pylori										
Other drugs for peptic ulcer and gastro-										

	LPD France							DA Germany		
	2017	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2017**	**2018**	**2019 etc**
oesophageal reflux disease (GORD)										

This table presents “late switching to alternative drugs” following interrupted use of ranitidine. A late switcher will be defined as a patient switching from treatment episodes of ranitidine to a treatment episode of alternative treatments but with a gap of more than 90 days between the end of the ranitidine treatment episode and the start of alternative treatment. The maximum gap between the end of the ranitidine treatment episode and the start of the alternative treatment can be maximum 1 year.

*”Switching to” will be expressed as proportion of total number of ranitidine switchers.

Table 5: Ranitidine treatment discontinuation (expressed as number of discontinuation per 1,000 persons)

	LPD_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP
By time						
2017						
Q1						
Q2						
Q3						
Q4						
2018						

	LPD_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP
Q1						
Q2						
Q3						
Q4						
2019						
Q1						
Q2						
Q3						
Q4						

	LPD_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP
2020						
Q1						
Q2						
Q3						
Q4						
2021						
Q1						
Q2						
Q3						

	LPD_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP
Q4						
2022						
Q1						
Q2						
Q3						
Q4						
Pre-referral						
In-referral						
Post-referral						

	LPD_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP
By details of previous Rantidine use						
Ranitidine cumulative exposure in days Cum days_Q1 Cum days_Q2 Cum days_Q3 Cum days_Q4						
Ranitidine dose at start of ranitidine initiation during follow-up: - <1 PDD/DDD - 1 PDD/DDD - 1PDD/DDD						
Indication of use:						

	LPD_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP
- GERD - Peptic ulcer - Peptic Ulcer with H Pylori - Gastritis/duodenitis - Gastritis/duodenitis with H Pylori - Zollinger Ellison Syndrome - Dyspepsia/Indigestion						
Age group: <2 years 2-11 years 12-18 years						

	LPD_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP
<=10 years >10-<=20 years >20-<=30 years >30-<=40 years >40-<=50years >50-<=60 years >60-<=70 years >70-<=80 years >80-<=90 years >90 <18 years 18<75 years						

	LPD_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP
≥ 75 years						
Sex: Female Male						
Formulation Oral Parenteral						

A similar table will be generated for the patients permanently discontinuing treatment with ranitidine during the complete study period

Table 6: Incidence of ranitidine and alternative medicines (expressed as number of new users per 1000 persons with the condition of interest) in patients with a medical history of any of the conditions for which ranitidine (or alternative drugs) is indicated. (only use in the 180 days following first diagnosis will be considered)

LPD France								
	H2RA	**Cimetidine**	**Famotidine**	**Nizatidine**	**Roxatidine**	**PPI**	**Omeprazole**	**Pantoprazole***
Indication of interest: GERD								
Pre-referral								
In-referral								
Post-referral								
Age group:								

LPD France								
	H2RA	**Cimetidine**	**Famotidine**	**Nizatidine**	**Roxatidine**	**PPI**	**Omeprazole**	**Pantoprazole***
<2 years 2-11 years 12-18 years <=10 years >10-<=20 years >20-<=30 years >30-<=40 years >40-<=50years >50-<=60 years >60-<=70 years >70-<=80 years								

LPD France								
	H2RA	**Cimetidine**	**Famotidine**	**Nizatidine**	**Roxatidine**	**PPI**	**Omeprazole**	**Pantoprazole***
>80-<=90 years >90 <18 years 18<75 years ≥ 75 years								
Sex: Female Male								
Formulation Oral								

LPD France								
	H2RA	**Cimetidine**	**Famotidine**	**Nizatidine**	**Roxatidine**	**PPI**	**Omeprazole**	**Pantoprazole***
Parenteral								
Etc.								

Table 7: Clinical characteristics at time of treatment initiation of ranitidine or alternative drugs during study follow-up

Incident ranitidine Use – proportion of conditions in 14 days prior to treatment start	**LPD_ France**	**DA_ Germany**	**IMRD**	**IPCI**	**LPD_ Belgium**	**SIDIAP**
Ordened by frequency (top 30)	Heartburn (13%)	Dyspepsia (20%)	Nausea (20%)	Nausea (20%)	Reflux disease (20%)	Dyspepsia (20%)
	Dyspepsia (6%)	Hypertension (15%)	Coughing (5%)	Urinary tract infection (15%)	Melaena (9%)	Duodenal Ulcer (15%)
	Pyrosis (3%)	Vomiting (3%)	Diarrhea (7%)	Pyrosis (12%)	Weight loss (4%)	Helicobacter pylori infection (3%)
	Myocardial infarction (0.5%)	Stress Ulcer (2%)	Pyrosis (12%)	Diarrhea (7%)	Sore throat (3%)	Anorexia (3%)
	Gastric bleeding (0.5%)	Urinary tract infection (2%)	Urinary tract infection (15%)	Coughing (5%)	Wrist ankle (3%)	Anorexia (3%)
Incident cimetidine Use – proportion of conditions in 14 days prior to treatment start						