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

EMA/2017/09/PE

Final Study Report V1.1

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PASS Information

Section	Description
Title	Study of exposure and use patterns of alternatives to ranitidine-containing medicines in patients treated with ranitidine
Version identifier of the final study report	V1.1
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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 anti-flatulents 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 gastroesophageal reflux disease (GORD)
Medicinal product	Multiple
Product reference	NA
Procedure number	EMA/2017/09/PE
Marketing authorisation holder(s)	Not applicable
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.
Countries of study	The Netherlands, Spain, UK, Belgium, Germany, and France

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Marketing authorisation holder(s)	NA
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ABSTRACT

Title

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

Version and Date

30th March 2023 – Version 1.1

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Key words

Ranitidine, Histamine 2 receptor antagonists, Proton Pump Inhibitors

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 (w/o H. 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.

On 12 September 2019, the European Commission triggered a referral procedure to evaluate the relevance of these findings, investigate 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) 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 was ongoing. Healthcare professionals have been asked to advise patients about alternative medicines when patients visited their prescribing physician for repeat prescriptions of ranitidine. Also, as ranitidine was no longer on the market, alternatives had to be chosen when there was an indication to newly prescribe ranitidine. 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 causing a need for 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(s) and objective(s)

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 is described as incident use and stratified by calendar year, by quarter, by referral period (pre-referral = September 2017- August 2019), in-referral = September 2019- March 2020, post-referral = April 2020 – March 2022), and by sex, age, country and data source.

2. In this study we describe the **switching to alternative medicinal products**, covering the following product classes:
   a. H2-receptor antagonists on class and substance level
   b. Proton-pump inhibitors (PPIs)
   c. other medicinal products for acid-related disorders

3. In this study we describe patients **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/indigestion) by age group, by sex, by prior usage patterns of ranitidine (e.g. duration of use, dose) and by country and data source.

4. In this report we **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- August 2019), in-referral = September 2019 - March 2020, post-referral = April 2020 – March 2022), age group, by sex, by formulation, and by country and data source.

Study design

A retrospective population-based cohort study was conducted using electronic health care records from databases from six European countries. Data was extracted over a study period of 1st January 2017 until 1st January 2023 to cover the ranitidine pre and post referral periods. Thus the study period spanned a larger time window than the referral periods. Analysis was done by calendar year (2017-2022) but also by referral period using the exact time windows as described above (under research questions/objectives).

Subjects and study size

The study population consisted of all persons with observation time during the study period. There were in total 45,456,150 individuals (21,463,677 in DA Germany; 781,905 in LPD Belgium; 10,011,441 in LPD France; 6,617,777 in SIDIAP (Spain); 4,695,649 in IMRD (UK) and 1,885,701 in IPCI (Netherlands (NL)).

Variables

Incident drug use (of ranitidine and alternative drugs) was expressed as the number of new users (no exposure within previous 365 days) per 1,000 person years (PY). For each database, stratum specific estimates were presented according to calendar year, quarter, referral period (pre-, in- and post-referral), age category and sex.

Discontinuation was expressed as the number of patients identified as discontinuing ranitidine treatment per 1,000 ranitidine users. A patient was defined as discontinuing ranitidine treatment in case there was a gap of at least 90 days after the end date of the last ranitidine episode without start of an alternative medication. In a sensitivity analysis, this minimum gap was extended to at least 365 days which was called “long-term discontinuation”.

Switching to alternative medications other than ranitidine was expressed as the number of patients identified as switching treatment per 1,000 ranitidine users.

Incident drug use was also explored in a cohort of patients newly diagnosed with conditions for which use of ranitidine was indicated prior to suspension. For estimation of the incidence drug use in the 180 days following the first diagnosis of interest, the numerator consisted of the number of incident users in this interval and the denominator consisted of the person time of patients with the indication of use in the 180 days following the first diagnosis of interest.

Key results

During the study period, 385,273 new users of ranitidine were observed of which the majority (304,968) occurred during the pre-referral period. The number of new ranitidine users decreased substantially in the in-referral and the post-referral period.

Most ranitidine users were female across all databases and across the periods (pre-, in- and post-referral period), and most users were between 18-74 years. Use of ranitidine mainly consisted of oral use which coincides with the fact that primary care databases were used.

The indication of use (based on predefined definitions) was often missing (in <=15% of users of ranitidine, predefined indications of use could be identified). For those prescriptions where indication of use was available, it mainly consisted of gastritis without H. Pylori or GERD.

Amongst the available H_2RA, ranitidine was most frequently prescribed with incidence rates ranging between 0.7-9.9/1000 PY in 2017. These numbers decreased almost to 0/1,000 PY in the post-referral period. Of all drugs of interest, PPIs was the drug class which was most frequently prescribed with incidence rates varying between 20.9-56.2/1,000 PY in 2017. During the in-referral period, an increase

of use of PPIs was observed which stabilized or decreased during the post-referral period (April 2020 - March 2022).

The incidence of switching from ranitidine to alternative drugs increased with calendar time especially as of 2019 a sharp increase was observed up to 2020. Individuals mainly switched from ranitidine to PPIs. After 2020, the proportion of individuals that switched decreased again, especially in IPCI (NL), LPD Belgium and DA Germany. Switching to other H_2RA was also observed but this proportion was much lower and was mainly observed in IMRD (UK), IPCI (NL) and to a lesser extend in DA Germany and SIDIAP (Spain).

The incidence of ranitidine users who discontinued therapy was comparable for LPD Belgium, LPD France, DA Germany and IPCI (NL) (range of 270-380/1,000 users at start of follow-up) whereas the incidence of ranitidine discontinuation was the lowest for IMRD (UK) (i.e., 133/1,000 users at start of follow-up). For most of the databases, the rate of discontinuation remained relatively stable over time and decreased as of 2021. The incidence of long-term discontinuation decreased as of 2019 for all databases except SIDIAP (Spain) where a decrease was observed for 2021. Overall, long-term discontinuation rates are much lower compared to the discontinuation rate defined by a gap of 90 days following the end date of last ranitidine episode.

When investigating how newly diagnosed individuals with conditions for which ranitidine was indicated prior to suspension, mainly PPIs were prescribed with incidence rates varying between 346/1,000 PY - 809/1,000 PY at the start of the study and incidence rates of 126/1,000 PY – 525/1,000 PY in 2022. Initiation of H_2RA was much lower with an incidence rate of 19/1,000 PY - 195/1,000 PY in 2017 to an incidence of 1.9/1,000 PY – 28.6/1,000 PY in 2022. Similar results were observed for ranitidine (which was the most prescribed H_2RA) with incidence rates decreasing to almost 0 in 2022.

The results from the time series analysis report a steep decrease in incidence of ranitidine prescribing, which started in July 2019 for DA Germany, IPCI (NL) and IMRD (UK) while for LPD Belgium and LPD France this decrease started in February 2019.

Discussion

In this study, we report that ranitidine was the most frequently prescribed H_2RA with incidence rates ranging between 0.7-9.9/1,000 PY in 2017. These numbers decreased almost to 0/1,000 PY in the post-referral period. Of all drugs of interest, PPIs were the drug class which was most frequently prescribed with incidence rates varying between 20.9-56.2/1,000 PY in 2017. During the in-referral period, an increase of use of PPIs was observed which stabilized or decreased during the post-referral period (April 2020 - March 2022). In patients newly diagnosed with conditions for which use of ranitidine or alternative drugs was indicated, mainly treatment with PPIs was initiated whereas initiation of H_2RA was much lower. Our findings are in line with results from other research groups also reporting a decrease in use of H_2RA in favour of PPIs. This tendence was already observed before the referral period and became stronger following the suspension of ranitidine. (1-4)

As for all observational research, our study has limitations and strengths. Our main limitation relates to the availability of data within the different data sources. Indeed, the indication of use was not always coded, which resulted in a high proportion of patients for whom the indication was unknown. Also, not all information on dosing was available and over the counter (OTC) use of H_2RA as well as use of H_2RA in secondary care was missing. Also, this report is based on prescription data and not dispensing data and we might thus overestimate ranitidine use as well as use of other alternative drugs.

Our main strength is the fact that we used real-world data on large datasets from multiple countries with source data mapped to the OMOP common data model. This methodology allowed us to optimize our research and to obtain the data in a fast and efficient way. Also, results are not only presented by means of a report, but all results can be accessed by the web application.

Conclusion

In this study, we report a decrease of ranitidine use during the study period with incidence rates almost decreasing to 0 in the post-referral period. Of potential alternative drugs to ranitidine, use of PPIs was the highest and use increased during the in-referral period but either stabilized or decreased during the post-referral period depending on the database being investigated. The incidence of switching from ranitidine to alternative drugs increased with calendar time especially as of 2019. Individuals mainly switched from ranitidine to PPIs. After 2020, the proportion of individuals that switched decreased again, especially in IPCI (NL), LPD Belgium and DA Germany which might be due to the very small group of remaining ranitidine users. In patients newly diagnosed with conditions for which use of ranitidine or alternative drugs is indicated, mainly treatment with PPIs was initiated whereas initiation of H_2RA was much lower.

1 List of Abbreviations

Abbreviation	Definition
API	Active Pharmaceutical Ingredient
CDM	Common Data Model
CHI	Catalan Health Institute
CHMP	Committee for Medicinal Products for Human Use
DDD	Defined Daily Dose
DHPC	Dear Healthcare Professional Communications
ECL	Enterochromaffin-like
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCePP	European Network of Centres for
FDA	Food and Drug Administration
GERD	Gastro-esophageal reflux disease
GP	General Practitioner
H_2	Histamine 2
H_2RA	Histamine 2 Receptor Antagonists
H. Pylori	Helicobacter Pylori
ICH	International Conference on Harmonisation
ISO	International Standard Organisation
IARC	International Agency for Research on Cancer
IMRD	IQVIA Medical Research Data
IPCI	Integrated Primary Care Information
LPD	Longitudinal Patient Database
NDMA	N-Nitrosodimethylamine
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OTC	Over The Counter
QMS	Quality Management System
PCT	Primary Care Teams
PDD	Prescribed Daily Dose
PPIs	Proton pump inhibitors
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Person Years
SIDIAP	Information System for Research in Primary Care
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

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4 Milestones

Milestone	Planned date
Approval Study Protocol by EMA	16th September 2021
Registration in the EU PAS register	2nd December 2021
Start of data collection	1st January 2017
End of data collection	1st January 2023
Final study report provided to EMA	28th February 2023
Manuscript to be provided to EMA	28th April 2023

5 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. (5, 6) 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. (7) 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, on 12 September 2019 the European Commission triggered 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) 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.

6 Research Questions and Objectives

The aim of this project was 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 were:

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, indication of use, age group, sex, formulation, country/data source.
2. To describe ***switching to alternative medicinal products***, covering the following product classes: H2 receptor antagonists (H_2RA) on class and substance level, medicinal products containing proton-pump inhibitors (PPIs), on class and substance level, and other medicinal products for acid-related disorders, on class level.
3. To describe ***patients permanently discontinuing treatment*** with ranitidine-containing medicinal products without switching to alternative medicines.
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).

7 Amendments and updates

The following changes were done in the statistical analysis plan, after the protocol was approved and will be reflected as protocol amendments.

Topic	Justification	Protocol amendment
Use of H_2RA for reason of hypersensitivity is excluded	Not relevant in GP setting	Yes
Cumulative dose of H_2RA and alternatives is removed	Not relevant for these research questions and to avoid crowding of the dataset	Yes

8 Research Methods

8.1 Study Design

A retrospective population-based cohort study was conducted using electronic health care records from six databases from six European countries. This cohort was 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.

This study was conducted in six European countries where ranitidine was available: 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). (8)

8.2 Setting

8.2.1 Study Time Period

As this study covers a time frame of 2 years prior to initiation of the referral (September 2017- August 2019) (pre-referral period), a time period of 2 years after initial CHMP recommendation for suspension which was April 2020 (April 2020 – March 2022) (post-referral period), and the period between initiation and finalisation of the referral (in-referral period, September 2019 - March 2020), data was 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 started at the start of the study period or the date on which the patient entered the study population and contributed active follow-up time, whichever came last. Follow-up ended at the end of the observation period or end of study period whichever came first.

8.3 Subjects

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

8.3.1 Patient Selection

From the study population, we identified (1) patients exposed to any of the drugs of interest (H_2RA, PPI and other medicinal products for acid-related disorders) (see Addendum 1 – List of ATC codes). Cohorts were constructed for patients exposed to each individual ingredient as well as to the respective drug class (H_2RA (excluding ranitidine), PPIs and antacids).

To describe the drug utilisation patterns of new starters of alternatives to ranitidine (research objective 4), we also (2) defined 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 was defined according to the presence of relevant OMOP Condition Concepts (SNOMED-CT) and drug use.

8.3.1.1 Inclusion criteria

The inclusion criteria were:

- All patients with an active registration status during the study 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.

8.3.1.2 Exclusion criteria

Patients were excluded if they had missing age or sex. No other exclusion criteria were applied.

8.4 Exposures of interest

From the study population, a cohort was 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 (Addendum 1 – list of ATC codes). The Standardised Vocabularies also provide a map to ATC codes if this is of value. Cohorts were 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 (see Table 1 Drug exposure table variables provided in the CDM).:

Table 1 Drug exposure table variables provided in the CDM

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.

From the Drug exposure table, the duration of use as well as the Prescribed Daily Dose (PDD) was calculated.

The duration of use of each individual prescription/dispensing is derived from the DRUG_EXPOSURE table in the CDM which contains the drug_exposure_start_date and the drug_exposure_end_date. The drug_exposure_start_date and the drug_exposure_end_date 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.

From the individual prescriptions/dispensings, treatment episodes were calculated which were the sum of the duration of the individual prescriptions/dispensing 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, signalled the end of the treatment episode. The 30-days cut-off is in line with what was also used by other research groups investigating trends in acid suppressant drug prescriptions in primary care (9).

If dosing instructions (= Sig) were available, the PDD was the number of units per day multiplied by the strength. If dosing instruction were missing, the PDD was 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 was missing, the dose was estimated using the Defined Daily Dose (DDD) as proxy. (10)

8.5 Outcomes

Incident drug use was defined as the number of new users per 1,000 person years. An incident user was 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 were presented separately according to calendar year, quarter, referral period (pre-referral = September 2017- August 2019, in-referral = September 2019 - March 2020, post-referral = April 2020 - March 2022), age category and sex. Incident drug use was 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.

Discontinuation of ranitidine treatment: A patient was defined as discontinuing ranitidine treatment in case there was a gap of at least 90 days following a ranitidine episode during which no new episode with use of ranitidine or alternative treatment started. In addition, this gap was extended to at least 365 days to take into account “long-term discontinuation”.

Switching from ranitidine to alternative medicines (H_2RA, PPI or other medicinal products for acid-related disorders) was categorized as i) *early switching* meaning a new treatment started shortly after an exposure of ranitidine or with a short overlap. The new treatment could start maximum 15 days before the end of ranitidine exposure and no later than 90 days after. Overlap of more than 15 days of use of ranitidine with use of alternative medicines was not considered as treatment switch. ii) *late switching* from ranitidine to alternative medicines was considered in case there was a gap of more than 90 but less than 365 days.

8.6 Variables

To meet the study objectives, the following parameters were obtained from the selected data sources and analysed:

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

8.6.1 Demographics

Sex was regarded as a fixed covariate throughout the study period.

Age was assessed at the start of each calendar year. Age categories of 10 year were used. To provide insight in the use of ranitidine in the elderly age was in addition categorized into <18 years, 18<75 years and ≥ 75 years. As use of ranitidine in children was very low, no further categorisation of the group with age below 18 was done.

8.6.2 Indication of use

All indications of use of interest were defined according to relevant OMOP Condition Concepts (SNOMED-CT) prior to the first prescription of ranitidine or alternatives to ranitidine (i.e., other H_2RA, PPIs and other medicinal products for acid-related disorders) during study follow-up. (8)

The indication of use was 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 in each of the three periods (pre-referral, in-referral and post-referral).

The indication of use for ranitidine treatment was 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. Originally, it was also planned to investigate the use of ranitidine or other H_2RA to prevent hypersensitivity in patients receiving chemotherapy. However, as this study used primary care data, where detailed information on chemotherapy and related prophylaxis is likely to be missing, this indication of use was removed from the protocol (see protocol version 3.0).

Whether a condition coincides with an infection of H. Pylori was either derived from the SNOMED CT describing presence of H. Pylori (see Addendum 1 - Codes for indication of use) or was 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 (see Addendum 1 - Codes for indication of use).

8.6.3 Clinical characteristics at time of treatment initiation

The previous paragraph defines which indications of use were investigated. However, as ranitidine (and alternative medicines) might be used for other (off-label) indications, we also explored 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.

8.7 Data Sources

For this study, we included 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 databases have mapped their data to the OMOP CDM. Characteristics of these databases for the total number of individuals and database updates have been described in Table 2 Characteristics of databases:

Table 2 Characteristics of databases

Database	Managing Organisation	Country	Individuals	Database date range
LPD Belgium	IQVIA	Belgium	1.1 M	2012 - present
LPD France	IQVIA	France	17.4 M	2012 - present
DA Germany	IQVIA	Germany	40.8 M	1992 - present
UK IMRD	IQVIA	UK	14.0 M	1994 - present
IPCI	Erasmus MC	Netherlands	2.8 M	2006 - present
SIDIAP	IDIAP Jordi Gol	Spain	7.9 M	2006 - present

Databases consist of individuals with active follow-up and historical patients

Integrated Primary Care Information (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands. (11, 12) 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 2006. (11) The median follow-up is 4.7 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. The Governance Board approved use of IPCI data for this study. (11)

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) managed by the Catalan Health Institute (CHI), consisting of GPs, nurses and other clinical and non-clinical staff. (13) The CHI 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 CHI 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 CHI, 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. The Scientific and an Ethics Committee approved use of SIDIAP data for this study.

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. (14) 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. An independent Scientific Review Committee approved use of IMRD UK data for this study.

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. (15) 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. (16) 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.

8.8 Study 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 was tested. Therefore, sample size calculation for the ability to reject a null hypothesis given an effect size was not conducted.

8.9 Data transformation

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 an R package was developed that contains all the functionality needed for this study.

Each data partner executed this R package against their database to generate the data for the drugs of interests, indications etc. After review of the results the data custodian sent them to the coordinating centre (Erasmus MC). The results from all six databases were combined in tables and figures presented in this study report.

8.10 Statistical methods

8.10.1 Main summary measures

Categorical variables were described by the number and percentage of patients in each category. The number of patients with missing data for key variables were reported and no imputation was performed to handle missing data (apart from treatment duration that was specified previously). All results are presented by database separately. To prevent the identification of individuals, cells containing low frequency counts of (1-5) were suppressed. Also proportions and incidences derived from these low counts are not displayed in tables or figures.

8.10.2 Descriptive analysis

8.10.2.1 Ranitidine cohort characteristics

Demographic characteristics, indications and characteristics of exposure were presented for ranitidine users in the three referral periods (pre-, in- and post-referral) for each database (and thus by country).

- The pre-referral period was defined as the period from September 2017 - August 2019.
- The in-referral period consisted of the period between September 2019-March 2020.
- The post-referral period consisted of the period between April 2020 - March 2022.

8.10.2.2 Incidence of drug use (ranitidine or alternative drugs)

Incidence drug use was defined as exposure to the drug of interest and no exposure within the previous 365 days. Incident drug use was expressed as the number of users per 1,000 person years. For each database (and thus by country), stratum specific estimates were presented separately according to calendar year, quarter, referral period (pre-, in- and post-referral), age category and sex.

8.10.2.3 Ranitidine discontinuation

Discontinuation was expressed as the number of patients identified as discontinuing ranitidine treatment per 1,000 ranitidine users. Incidences were presented per calendar year, quarter, and referral period. For each database (and thus by country), stratum specific estimates were presented according to age categories, sex, formulation, and usage patterns of ranitidine (duration of use, dose).

8.10.2.4 Ranitidine switching

Switching onto alternative medications other than ranitidine was expressed as the number of patients identified as switching treatment per 1,000 ranitidine users. Incidences were presented per calendar year, quarter, and referral period. For each database (and thus by country), stratum specific estimates were presented separately according to age category, sex, formulation, and usage patterns of ranitidine (duration of use, dose).

8.10.2.5 Drug utilisation patterns of patients diagnosed with the indication of use of ranitidine (or alternatives)

Amongst 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), the incidence of use of ranitidine as well as alternatives to ranitidine (other H_2RA, PPIs and acid suppressant medications) was calculated. For estimation of the incidence drug use in the 180 days following the first diagnosis of interest, the numerator consisted of the number of incident users in this interval. The denominator consisted of the person time of patients with the indication of use in the 180 days following the first diagnosis of interest. Incidence rates were described by database per calendar year, quarter and referral period and further stratified by age and sex.

8.10.2.6 Timeseries analysis

A Joinpoint regression model was used to investigate changes in prescribing patterns of ranitidine over calendar time. Incidence rates per quarter were analysed allowing a maximum of 3 join points.

8.10.2.7 Missing values

No imputation of missing values was applied; only those with relevant information were included.

8.10.3 Sensitivity analysis

Sensitivity analyses which were planned for this study are described in Table 3 Sensitivity analyses. Sensitivity analysis consisted of broadening the window in which we search for the indication of use from 180 to 365 days prior to the prescription date. With regard to discontinuation, the minimum gap to define treatment discontinuation was extended from 90 to 365 days. Other sensitivity analyses were planned namely an analysis where we explored permanent discontinuation, but this proofed not to be usefully as mainly driven by the fact whether or not the patient had sufficient follow-up time. In addition, the analysis where late switching was assessed in a window of 730 days instead of 365 days proofed not to provide additional value.

Table 3 Sensitivity analyses

Main Definition	Alternative Definition
Indication of use	• 365 days prior to treatment initiation
Ranitidine discontinuation	• A sensitivity analysis was included in which there needed to be a period of at least 365 days with no use of ranitidine or alternative treatment.

8.11 Quality Control

IQVIA Quality Management System (QMS)

As the coordinating centre for this collaboration, the IQVIA QMS was 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 with the appropriate global procedure.

EMC Quality Management System (QMS)

This project will be executed setting a high-quality standard regarding 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 in the 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 is submitted to the EUPAS Register® and the final study report will be uploaded and available for consultation in the EUPAS Register®

For this study, we used 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 followed 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.

9 Results

In the following sections, we focus on the main findings of this study. Data are further illustrated by graphs where needed. Additional tables and figures are also added to an appendix of this report.

All results (with tables and figures) can also be accessed by the web application, which has been created for this project. This consists of three parts:

- https://mi-erasmusmc.shinyapps.io/Ranitidine2Part1/: Incidence of drug use (in total population as well as in persons with indication), descriptives of ranitidine users, clinical characteristics of ranitidine users, time series analysis
- https://mi-erasmusmc.shinyapps.io/Ranitidine2Part2/: Switching to alternative medications
- https://mi-erasmusmc.shinyapps.io/Ranitidine2Part3/: Discontinuation of ranitidine use

9.1 Number of individuals and ranitidine users during study period

The number of active individuals (i.e. contributing follow-up time) during the study period and the number of ranitidine users for each database are presented in Table 4 Number of individuals and ranitidine users by database and referral period. The total number of individuals consisted of more than 45 million. The database that contributed most of the individuals was DA Germany (47%) (Table 4 Number of individuals and ranitidine users by database and referral period). The total number of ranitidine users was 304,968 in the pre-referral period. Compared with the pre-referral period, the total number of ranitidine users was decreasing substantially in the in-referral (n = 38,691) and post-referral period (n = 14,614). This pattern was consistent in all databases.

Table 4 Number of individuals and ranitidine users by database and referral period

Database	Total individuals during study period	Ranitidine users		
		Pre-referral period	In-referral period	Post-referral period
DA Germany	21,463,677	27,821	3,128	1,601
IPCI	1,885,701	22,709	1,843	1,539
LPD Belgium	781,905	14,693	2,042	157
LPD France	10,011,441	20,256	2,719	1,510
SIDIAP	6,617,777	81,284	4,776	28
UK IMRD	4,695,649	138,205	24,183	9,779

Database	Total individuals during study period	Ranitidine users		
		Pre-referral period	In-referral period	Post-referral period
Total	**45,456,150**	**304,968**	**38,691**	**14,614**

Ranitidine users – Total number of persons using ranitidine. A person with several ranitidine exposures in a period is counted only once.
Pre-referral period = September 2017- August 2019, In-referral period = September 2019 - March 2020, post-referral period = April 2020 - March 2022

9.1.1 Characteristics of ranitidine users

The demography of ranitidine users (by referral period) is described in Table 5 Demographic characteristics of ranitidine users by database and referral period.

Table 5 Demographic characteristics of ranitidine users by database and referral period

Database			Pre-referral period		In-referral period		Post-referral period	
			N	(%)	N	(%)	N	(%)
LPD Belgium	Sex	FEMALE	8,932	60.79	1,226	60.04	95	60.51
		MALE	5,761	39.21	816	39.96	62	39.49
	Age (y)	<18	880	5.99	98	4.80	<5	
		18-74	11,866	80.76	1,640	80.31	117	74.52
		75+	1,947	13.25	304	14.89	37	23.57
LPD France	Sex	FEMALE	11,758	58.05	1,565	57.56	850	56.29
		MALE	8,406	41.50	1,142	42.00	652	43.18
		No matching concept*	92	0.45	12	0.44	8	0.53
	Age (y)	<18	470	2.32	46	1.69	15	0.99
		18-74	15,839	78.19	2,084	76.65	1,122	74.30
		75+	3,947	19.49	589	21.66	373	24.70
DA Germany	Sex	FEMALE	16,147	58.04	1,825	58.34	915	57.15
		MALE	11,613	41.74	1,292	41.30	675	42.16
		No matching concept*	61	0.22	11	0.35	11	0.69
	Age (y)	<18	736	2.65	69	2.21	27	1.69
		18-74	21,219	76.27	2,313	73.95	1,191	74.39
		75+	5,866	21.08	746	23.85	383	23.92
UK IMRD	Sex	FEMALE	83,835	60.66	14,666	60.65	5,904	60.37
		MALE	54,370	39.34	9,517	39.35	3,875	39.63
	Age (y)	<18	15,751	11.40	1,983	8.20	443	4.53
		18-74	96,378	69.74	17,135	70.86	7,175	73.37
		75+	26,076	18.87	5,065	20.94	2,161	22.10
IPCI	Sex	FEMALE	13,752	60.56	1,091	59.20	936	60.82
		MALE	8,957	39.44	752	40.80	603	39.18

Database			Pre-referral period		In-referral period		Post-referral period	
			N	(%)	N	(%)	N	(%)
	Age (y)	<18	2,064	9.09	182	9.88	314	20.40
		18-74	17,402	76.63	1,414	76.72	1,027	66.73
		75+	3,243	14.28	247	13.40	198	12.87
SIDIAP	Sex	FEMALE	54,041	66.48	3,187	66.73	17	60.71
		MALE	27,243	33.52	1,589	33.27	11	39.29
	Age (y)	<18	1,754	2.16	89	1.86		
		18-74	70,383	86.59	4,141	86.70	19	67.86
		75+	9,147	11.25	546	11.43	9	32.14

No matching concept meaning information on sex was missing.
Pre-referral period = September 2017- August 2019, In-referral period = September 2019 - March 2020, post-referral period = April 2020 - March 2022.

In all databases, within the ranitidine users, there were more female than male users and this pattern was consistent over the different referral periods. In all databases, the majority of users was aged between 18-74 (proportions of 65% or higher) and this was consistent across the different referral periods. Amongst users of ranitidine, children were the smallest group, especially in LPD France, DA Germany and SIDIAP (Spain).

9.1.2 Duration of use, dosing and type of formulation of ranitidine

Information on duration of use, type of formulation and dosing (expressed as PDD/DDD) by period is provided in Table 3 of the appendix. Duration of use was categorized into 4 categories: 1-15 days, 16-30 days, 31-100 days and more than 100 days. Although no clear differences in duration over the different periods (prereferral, referral and post-referral) could be observed, differences in categories of duration were observed between databases. For instance, high proportion (45%) of patients using ranitidine for 31-100 days was observed in DA Germany whereas proportion for this category was lower (11 to 38%) in the other databases. In all databases, parenteral use of ranitidine was low (<5% of all ranitidine use). Regarding dosing, in all databases (except for SIDIAP) where information on dosing was available, the majority of individuals received ranitidine in line with recommended DDD of the WHO (i.e., PDD/DDD of 1).

9.1.3 Indication of use of ranitidine by period

The indication of use was assessed in a window of 180 or 365 days (sensitivity analysis) of the first prescription of ranitidine during each of the referral periods. In these windows we checked for the presence of predefined SNOMED codes for the gastro-intestinal indications of interest.

Results by period are provided in Table 4 of the appendix. As first observation, it is clear that the indication of use of ranitidine is often missing within the different databases. Indeed, the indication of use was missing in almost 85% of all new users of ranitidine and the proportion of missing was the highest for IMRD (UK) (up to 95% missing). No differences in type of indication between periods were observed. However, differences between databases in type of indications were observed with highest proportions for treatment of gastritis without H. Pylori for LPD Belgium, LPD France, DA Germany and IMRD (UK) and highest proportion for treatment of GERD for SIDIAP (Spain) and IPCI (UK). By

extending look-back window to 365 days, the proportion of individuals with information on indication of use increased but no important differences in type of indication were observed.

We did not only investigate the indication of use based on predefined disease codes but also explored the type of conditions and procedures within a window of 14 days prior to the start of a prescription. The top 30 of disease codes (by database and by type of drug (ranitidine or alternatives) are provided in the appendix (Tables 5-11). And although the proportion of patients with predefined disease codes for the indication of interest was low, when exploring all potential disease codes within 14 days prior to the index date, it is clear that ranitidine (and alternative drugs) were prescribed for reason of gastro-intestinal complaints (see Table 6 Proportion of disease codes (top 5) for ranitidine within 14 days prior to the prescription date).

For this analysis, we decided to only look into a window of 14 days prior to the prescription and not using the window of 180 days (365 days for the sensitivity analysis) to reduce the risk of potential misclassification. Indeed, as can be observed in Table 6, the majority of disease codes refer to gastro-intestinal codes but also other codes such as hypertension, blood pressure finding etc were reported and this list of irrelevant disease codes would have increased using these larger time windows prior to the prescription, dispensing.

Table 6 Proportion of disease codes (top 5) for ranitidine within 14 days prior to the prescription date

DA Germany	IPCI	LPD Belgium	LPD France	SIDIAP	UK IMRD
Gastritis (14.1%)	Stomach ache (26.6%)	Gastritis (39.6%)	Upper abdominal pain (20.6%)	Epigastric pain (8.6%)	Patient review (15.1%)
Gastro-oesophageal reflux disease with esophagitis (8.1%)	Heartburn (9.4%)	Gastroesophageal reflux disease (24.9%)	Gastroesophageal reflux disease without esophagitis (17.8%)	Abdominal pain (4.6%)	Blood pressure finding (14.4%)
Essential hypertension (7.1%)	Localized abdominal pain (4.8%)	Essential hypertension (14.8%)	Essential hypertension (12.8%)	Non-ulcer dyspepsia (4.0%)	Administration (8.6%)
Inflammatory disorder of digestive tract (6.6%)	Stomach cramps (3.2%)	Esophagitis (10.9%)	Gastritis (9.5%)	Gastrointestinal infection (3.5%)	Abdominal pain (5.0%)
Gastroesophageal reflux disease without esophagitis (3.8%)	Generalized abdominal pain (3.2%)	Heartburn (7.3%)	Abdominal pain (7.1%)	Heartburn (2.7%)	Review of medication (4.7%)

9.2 Incidence of ranitidine use and alternative medicines over time

The incidence of ranitidine use for calendar time by database is presented in Table 7 Incidence of drug use by calendar year and in Figure 1 Incidence of ranitidine use over time.

Amongst the available H_2 receptor antagonists, ranitidine was most frequently prescribed with incidence rates ranging between 0.7-9.9/1000 PY in 2017. Use of ranitidine was the highest in LPD Belgium and IMRD (UK) (9.9 and 8.1/1,000 PY respectively) and the lowest in DA Germany (0.7/1,000 PY). Incident rates were decreasing to 0 in post-referral period in all databases. Use of other H_2RA such as cimetidine, famotidine and nizatidine was low or non-existing (Figure 2 Incidence of other H_2RA over time). And although use of other H_2RA was low, an increase over time was observed in IPCI (NL), SIDIAP (Spain) and IMRD (UK).

Incidence of PPI prescribing is described in Table 7 Incidence of drug use by calendar year and Figure 3 Incidence of PPI over time. Of all investigated drug classes, prescribing of PPIs was the most common with incidence rates varying between 20.9-56.2/1,000 PY in 2017. The incidence of PPI prescribing increased over time in LPD France, LPD Belgium and DA Germany whereas it remained stable in the other databases. Amongst the PPIs especially pantoprazole and omeprazole were prescribed.

Use of antacids ranged between 0.3-12.8/1,000 PY in 2017 with lowest use in DA Germany and highest use in IMRD (UK) (Figure 4 Incidence of antacids over time). This incidence remained stable or decreased in IPCI (NL) and IMRD (UK) respectively whereas it increased in LPD Belgium, DA France, SIDIAP (Spain) and DA Germany. Use of prostaglandins, combination therapy for H. Pylori eradication and use of other drugs for the treatment of peptic ulcers or GERD was low in all databases (i.e., incident drug use of <= 5/1,000 PY). (See appendix Figures 1-3)

Table 7 Incidence of drug use by calendar year

Ingredient	Database	Incidence per 1,000 PY					
		2017	2018	2019	2020	2021	2022
Ranitidine	DA Germany	0.69	0.74	0.71	0.11	0.04	0.02
	IPCI	4.60	4.40	3.64	0.61	0.26	0.04
	LPD Belgium	9.88	8.95	7.98	0.41	0.04	0.13
	LPD France	0.95	1.07	0.95	0.20	0.07	0.01
	SIDIAP	5.61	5.89	4.63	0.02	0.00	
	UK IMRD	8.08	8.17	7.19	1.02	0.17	0.03
Cimetidine	DA Germany	0.02	0.02	0.07	0.05	0.04	0.06
	IPCI	0.05	0.04	0.60	0.20	0.26	0.19
	LPD Belgium	0.08	0.03		0.00	0.00	

Ingredient	Database	Incidence per 1,000 PY					
		2017	2018	2019	2020	2021	2022
	LPD France	0.12	0.11	0.15	0.09	0.07	0.13
	UK IMRD	0.06	0.06	0.25	0.91	0.20	0.16
Famotidine	DA Germany	0.02	0.02	0.07	0.13	0.15	0.26
	IPCI	0.02	0.01	0.53	0.87	1.58	1.64
	LPD France	0.01	0.01	0.03	0.06	0.12	0.21
	SIDIAP	0.08	0.08	1.56	1.27	1.80	1.91
	UK IMRD	0.01	0.01	0.08	0.78	1.83	1.88
Nizatidine	IPCI			0.04	0.02		0.00
	LPD France		0.00	0.00	0.01	0.00	0.00
	UK IMRD	0.01	0.01	0.15	0.42	0.24	0.16
H2 no Ranitidine	DA Germany	0.03	0.04	0.14	0.17	0.19	0.32
	IPCI	0.07	0.05	1.01	0.91	1.80	1.80
	LPD Belgium	0.08	0.03		0.00	0.00	
	LPD France	0.13	0.13	0.18	0.15	0.18	0.33
	SIDIAP	0.08	0.08	1.56	1.27	1.80	1.91
	UK IMRD	0.07	0.07	0.46	1.64	1.98	2.10
H2 Class	DA Germany	0.72	0.77	0.78	0.23	0.22	0.33
	IPCI	4.58	4.44	3.85	1.21	1.91	1.83
	LPD Belgium	9.94	8.97	7.99	0.41	0.04	0.14
	LPD France	1.07	1.19	1.07	0.30	0.24	0.34
	SIDIAP	5.68	5.95	5.08	1.08	1.80	1.92
	UK IMRD	8.12	8.18	7.26	1.44	1.85	2.10
Omeprazole	DA Germany	4.52	4.57	4.82	4.76	5.13	7.08
	IPCI	29.87	28.91	29.10	25.11	23.37	22.05

Ingredient	Database	Incidence per 1,000 PY					
		2017	2018	2019	2020	2021	2022
	LPD Belgium	18.84	17.56	18.14	18.84	17.12	26.26
	LPD France	21.27	21.57	21.23	18.59	21.14	29.96
	SIDIAP	54.96	56.42	59.82	46.88	54.58	53.75
	UK IMRD	35.67	35.62	38.04	37.81	39.45	35.83
Pantoprazole	DA Germany	17.00	18.26	19.99	21.33	24.66	34.96
	IPCI	20.31	21.29	23.85	22.37	22.27	21.06
	LPD Belgium	35.13	36.24	41.15	45.07	43.70	70.45
	LPD France	7.99	8.39	9.05	9.43	11.11	15.30
	SIDIAP	2.48	2.43	2.54	2.29	2.59	2.55
	UK IMRD	0.65	0.56	0.63	0.80	0.69	0.57
Lansoprazole	DA Germany	0.08	0.08	0.08	0.09	0.09	0.11
	IPCI	0.09	0.07	0.09	0.09	0.07	0.07
	LPD Belgium	0.72	0.58	0.62	0.70	0.65	0.88
	LPD France	4.40	4.37	4.36	4.29	4.80	6.57
	SIDIAP	1.34	1.41	1.50	1.28	1.51	1.60
	UK IMRD	13.60	13.54	14.13	14.95	14.29	12.89
Rabeprazole	DA Germany	0.06	0.06	0.07	0.09	0.10	0.14
	IPCI	0.28	0.28	0.31	0.25	0.30	0.22
	LPD Belgium	0.06	0.08	0.06	0.05	0.07	0.11
	LPD France	2.91	2.79	2.70	2.65	2.69	3.45
	SIDIAP	0.61	0.60	0.59	0.55	0.61	0.57
	UK IMRD	0.06	0.07	0.08	0.09	0.07	0.06
Esomeprazole	DA Germany	1.42	1.51	1.82	2.04	2.64	3.87
	IPCI	2.59	2.62	2.42	2.39	3.18	3.56

Ingredient	Database	Incidence per 1,000 PY					
		2017	2018	2019	2020	2021	2022
	LPD Belgium	8.53	8.96	9.25	9.62	9.92	16.27
	LPD France	19.66	19.96	20.58	20.15	25.22	34.62
	SIDIAP	2.21	2.32	2.60	2.23	2.83	2.92
	UK IMRD	1.65	1.65	1.76	1.83	2.01	1.74
Dexlansoprazole	DA Germany	0.00	0.00			0.00	
PPI	DA Germany	20.90	22.26	24.45	25.83	29.75	42.25
	IPCI	45.45	45.58	47.62	42.90	41.89	40.50
	LPD Belgium	55.14	55.59	60.96	64.90	62.10	100.05
	LPD France	47.55	48.38	49.62	47.32	56.32	78.11
	SIDIAP	56.22	57.86	61.47	48.51	56.67	55.92
	UK IMRD	43.82	43.94	46.85	46.99	48.00	43.65
Antacids	DA Germany	0.31	0.33	0.42	0.50	0.53	0.78
	IPCI	12.05	12.53	12.87	11.14	11.40	11.09
	LPD Belgium	8.77	9.01	9.86	9.95	10.24	15.94
	LPD France	2.60	2.85	3.02	3.09	3.39	4.44
	SIDIAP	6.51	8.32	8.64	6.63	8.94	10.08
	UK IMRD	12.75	12.07	12.47	12.01	13.02	12.32
Prostaglandins	DA Germany	0.05	0.04	0.06	0.05	0.05	0.05
	IPCI	1.86	1.59	1.14	0.98	0.90	0.91
	LPD Belgium	0.04	0.04	0.04	0.04	0.10	0.08
	LPD France	1.20	0.94	0.01	0.00	0.01	0.01
	SIDIAP	0.26	0.28	0.21	0.11	0.08	0.08
	UK IMRD	0.08	0.04	0.05	0.02	0.02	0.02
	DA Germany	0.19	0.19	0.20	0.19	0.19	0.24

Ingredient	Database	Incidence per 1,000 PY					
		2017	2018	2019	2020	2021	2022
Combination therapy for eradication of Helicobacter pylori	IPCI	0.84	0.94	1.00	0.76	0.77	0.51
	LPD Belgium	0.08	0.10	0.15	0.16	0.22	0.32
	LPD France	0.58	0.63	0.69	0.63	0.81	1.06
	SIDIAP	1.08	1.83	2.41	1.84	2.92	3.28
Other drugs for peptic ulcer and GERD	DA Germany	0.47	0.65	0.80	0.87	1.05	1.48
	IPCI	1.21	1.24	1.21	1.27	1.32	1.19
	LPD Belgium	0.72	0.79	1.04	1.00	0.85	1.00
	LPD France	0.50	0.45	0.47	0.44	0.51	0.74
	SIDIAP	0.23	0.22	0.24	0.15	0.13	0.00
	UK IMRD	5.04	4.53	4.45	4.58	4.87	4.40

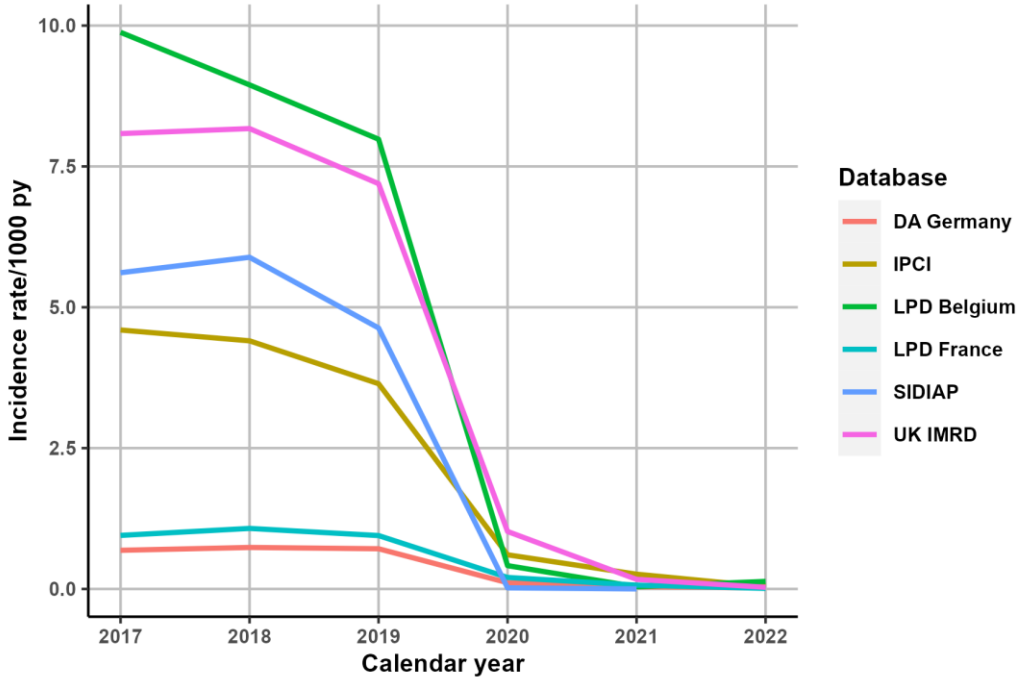

Figure 1 Incidence of ranitidine use over time

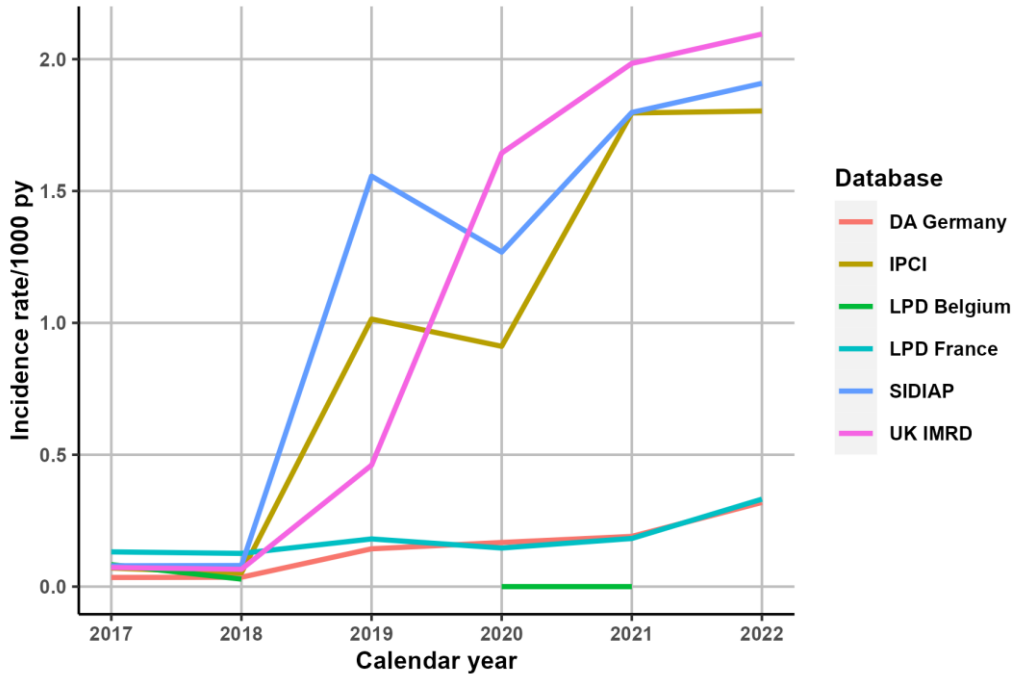

Figure 2 Incidence of other H_2RA over time

Legend: Incidence rates were not provided if the numbers of individuals with other H_2RA is <5.

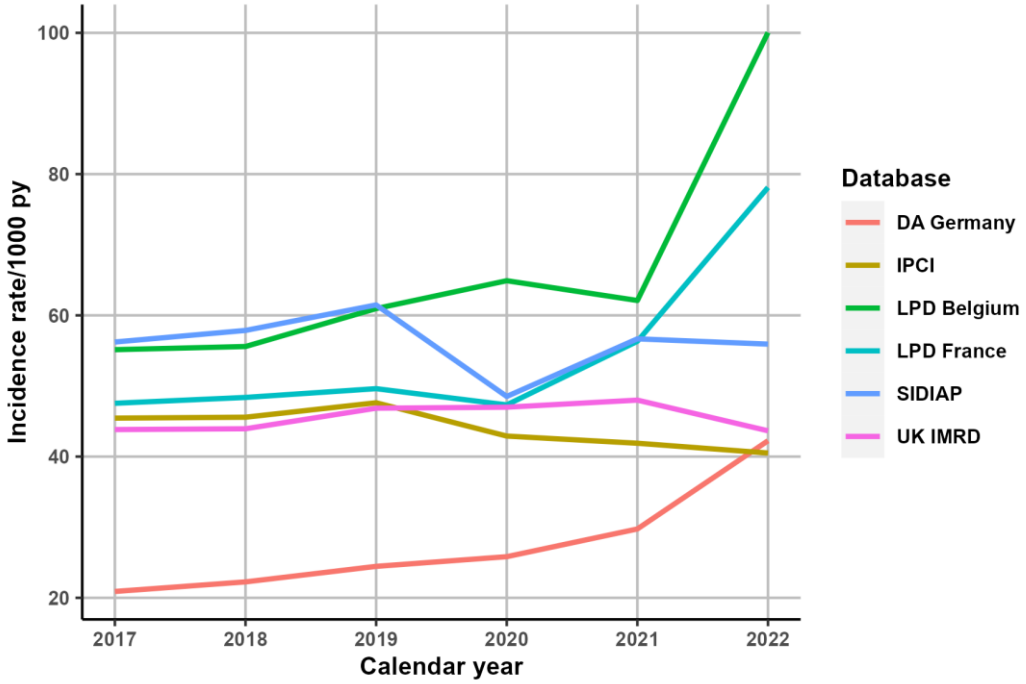

Figure 3 Incidence of PPI over time

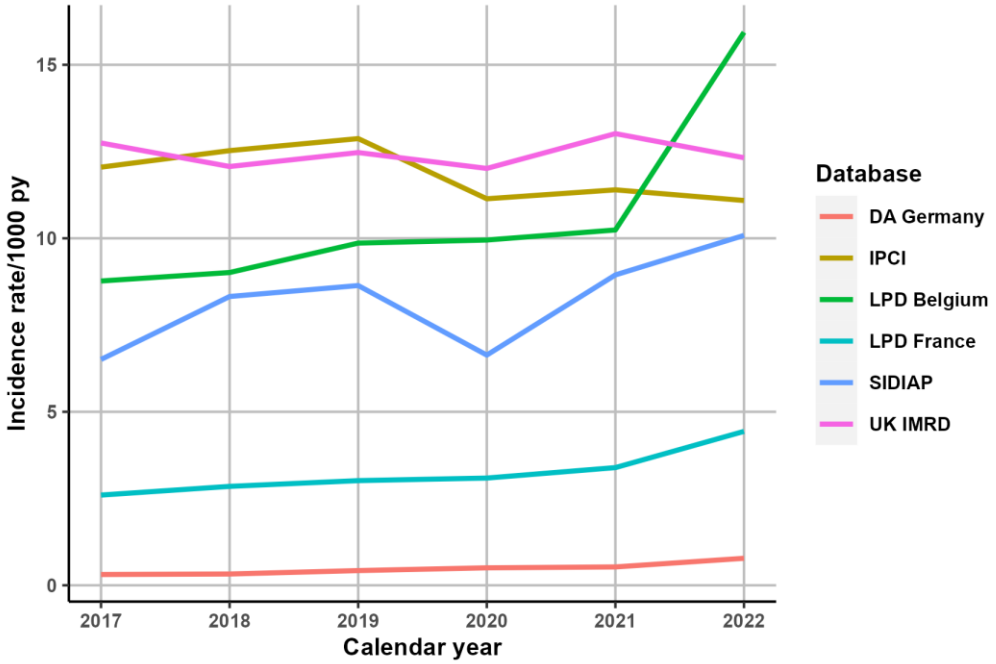

Figure 4 Incidence of antacids over time

The incidence of ranitidine by referral period is described in Table 8 Incidence of drug use by period and in Figure 5 Incidence of ranitidine by referral period. In all databases, use of ranitidine decreased considerably during the referral period (September 2019 - March 2020) and was very low or absent in the post-referral period. During the referral period, an increase of use of PPIs was observed which stabilized or decreased during the post-referral period (April 2020 - March 2022) (Figure 6 Incidence of PPIs by referral period). This trend was not as clear for the other drugs (prostaglandins, antacids, drugs for eradication of H. Pylori) of interest (See appendix Figures 4-8).

Table 8 Incidence of drug use by period

							Incidence per 1,000 PY
Ingredient	Period	DA Germany	IPCI	LPD Belgium	LPD France	SIDIAP	UK IMRD
Ranitidine	Pre-referral	0.77	4.51	9.03	1.06	5.85	8.23
	Referral	0.27	1.19	3.75	0.46	1.16	3.64
	Post-referral	0.06	0.37	0.10	0.11	0.00	0.31
Cimetidine	Pre-referral	0.02	0.05	0.03	0.11		0.05
	Referral	0.15	1.07	0.00	0.19		0.68
	Post-referral	0.04	0.22	0.00	0.08		0.53
Famotidine	Pre-referral	0.02	0.02		0.01	0.08	0.01
	Referral	0.17	1.19		0.09	3.27	0.22
	Post-referral	0.14	1.33		0.10	1.57	1.51
Nizatidine	Pre-referral				0.00		0.01
	Referral		0.09		0.01		0.36
	Post-referral		0.01		0.00		0.34
H2 no Ranitidine	Pre-referral	0.04	0.07	0.03	0.12	0.08	0.06
	Referral	0.30	1.92	0.00	0.27	3.27	1.18
	Post-referral	0.18	1.49	0.00	0.17	1.57	1.98
H2 Class	Pre-referral	0.80	4.55	9.05	1.17	5.92	8.25
	Referral	0.39	1.66	3.75	0.61	2.35	3.82
	Post-referral	0.22	1.67	0.10	0.26	1.53	1.59

Incidence per 1,000 PY

Ingredient	Period	DA Germany	IPCI	LPD Belgium	LPD France	SIDIAP	UK IMRD
Omeprazole	Pre-referral	4.52	28.20	17.49	20.79	55.19	35.08
	Referral	5.25	29.78	21.29	21.46	59.94	41.69
	Post-referral	4.96	23.31	17.72	19.92	49.57	37.76
Pantoprazole	Pre-referral	18.07	21.37	36.85	8.32	2.42	0.56
	Referral	22.22	25.38	47.29	9.72	2.57	0.76
	Post-referral	23.32	21.72	44.45	10.47	2.47	0.74
Lansoprazole	Pre-referral	0.07	0.08	0.61	4.24	1.42	13.35
	Referral	0.10	0.12	0.64	4.61	1.45	15.93
	Post-referral	0.09	0.08	0.67	4.57	1.43	14.32
Rabeprazole	Pre-referral	0.06	0.28	0.07	2.73	0.59	0.07
	Referral	0.09	0.34	0.05	2.78	0.58	0.10
	Post-referral	0.10	0.27	0.07	2.68	0.58	0.08
Esomeprazole	Pre-referral	1.56	2.52	8.71	19.55	2.36	1.65
	Referral	2.03	2.57	10.25	21.31	2.52	1.92
	Post-referral	2.44	2.87	9.93	23.19	2.61	1.92
Dexlansoprazole	Pre-referral						
	Referral						
	Post-referral	0.00					
PPI	Pre-referral	22.02	44.55	55.66	46.95	56.62	43.14
	Referral	27.19	49.72	69.98	51.34	61.45	51.60
	Post-referral	28.11	41.02	63.21	52.29	51.49	46.28
Antacids	Pre-referral	0.34	12.46	9.18	2.80	8.18	12.09
	Referral	0.53	13.34	10.93	3.41	7.98	12.87
	Post-referral	0.53	10.97	10.19	3.24	8.05	12.43

		Incidence per 1,000 PY					
Ingredient	Period	DA Germany	IPCI	LPD Belgium	LPD France	SIDIAP	UK IMRD
Prostaglandins	Pre-referral	0.05	1.46	0.05	0.70	0.26	0.05
	Referral	0.05	0.97	0.05	0.01	0.16	0.03
	Post-referral	0.05	0.91	0.08	0.01	0.09	0.02
Combination therapy for eradication of Helicobacter pylori	Pre-referral	0.20	0.93	0.11	0.64	1.93	
	Referral	0.19	1.07	0.16	0.70	2.37	
	Post-referral	0.19	0.71	0.20	0.73	2.49	
Other drugs for peptic ulcer and GERD	Pre-referral	0.67	1.20	0.85	0.47	0.23	4.48
	Referral	0.89	1.29	1.25	0.47	0.22	4.88
	Post-referral	1.01	1.29	0.85	0.49	0.12	4.70

Pre-referral period= September 2017- August 2019, referral period= September 2019- March 2020, post-referral period= April 2020 - March 2022

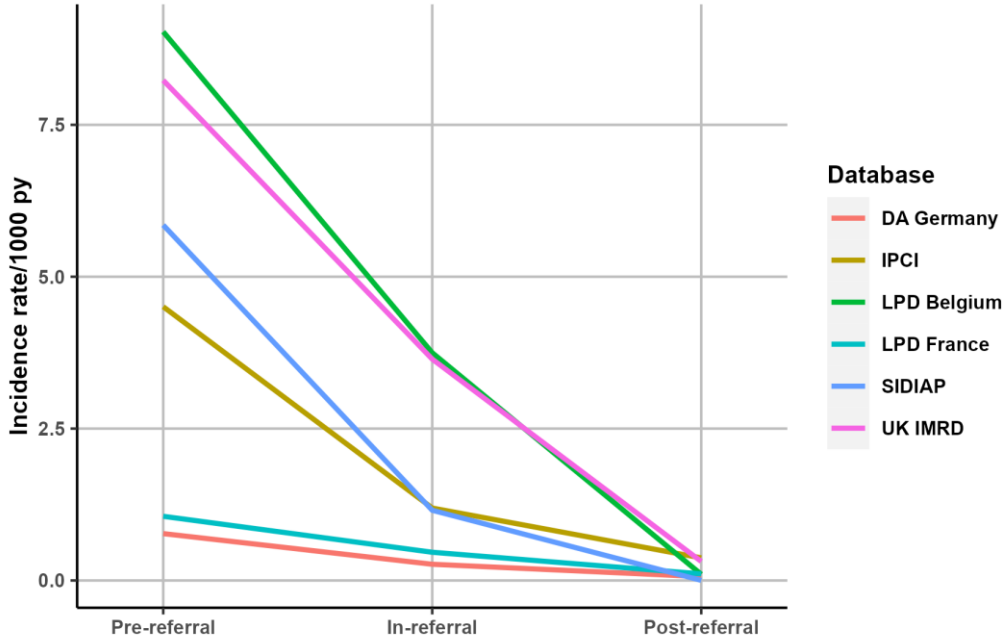

Figure 5 Incidence of ranitidine by referral period

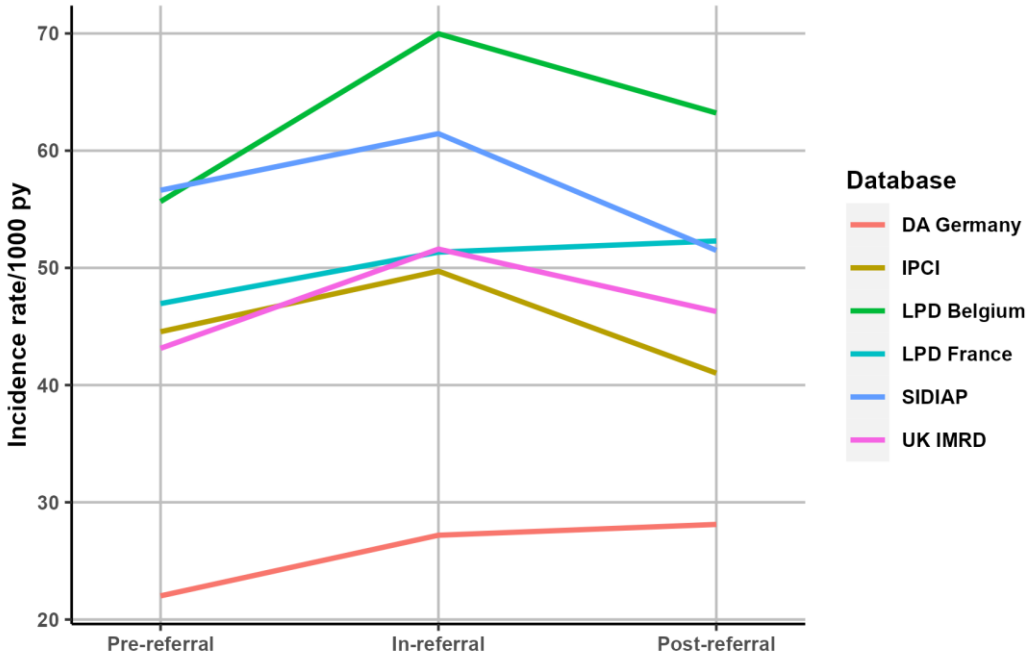

Figure 6 Incidence of PPIs by referral period

9.3 Incidence of ranitidine and alternative medicines by age and sex

When stratified by age, use of ranitidine was the lowest in children and use of ranitidine increased from the age of 60 on, especially in IMRD (UK) (Figure 7 Incidence of ranitidine, by age and calendar year).

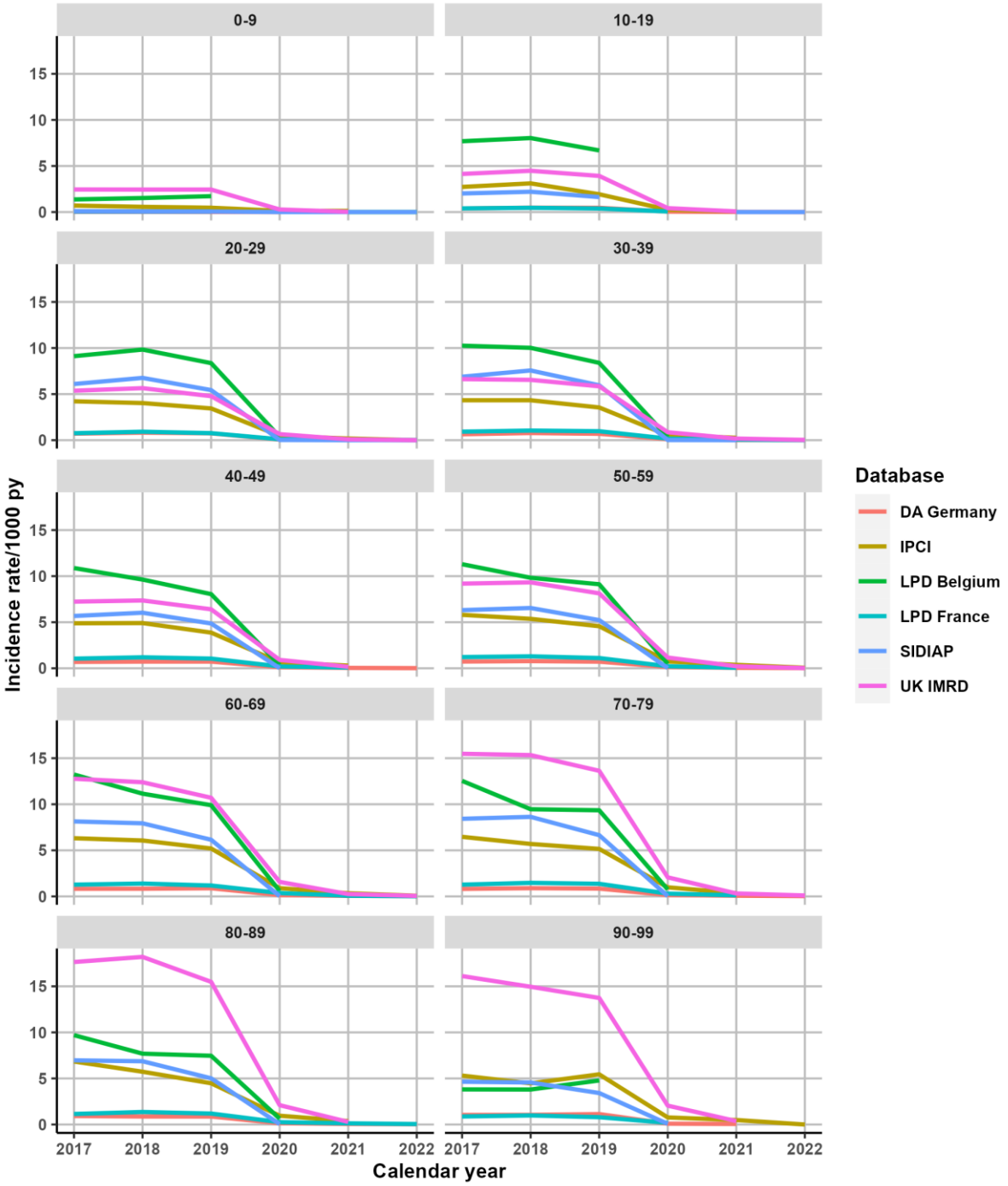

Figure 7 Incidence of ranitidine, by age and calendar year

Legend: Incidence rates were not provided if the numbers of individuals with ranitidine is <5.

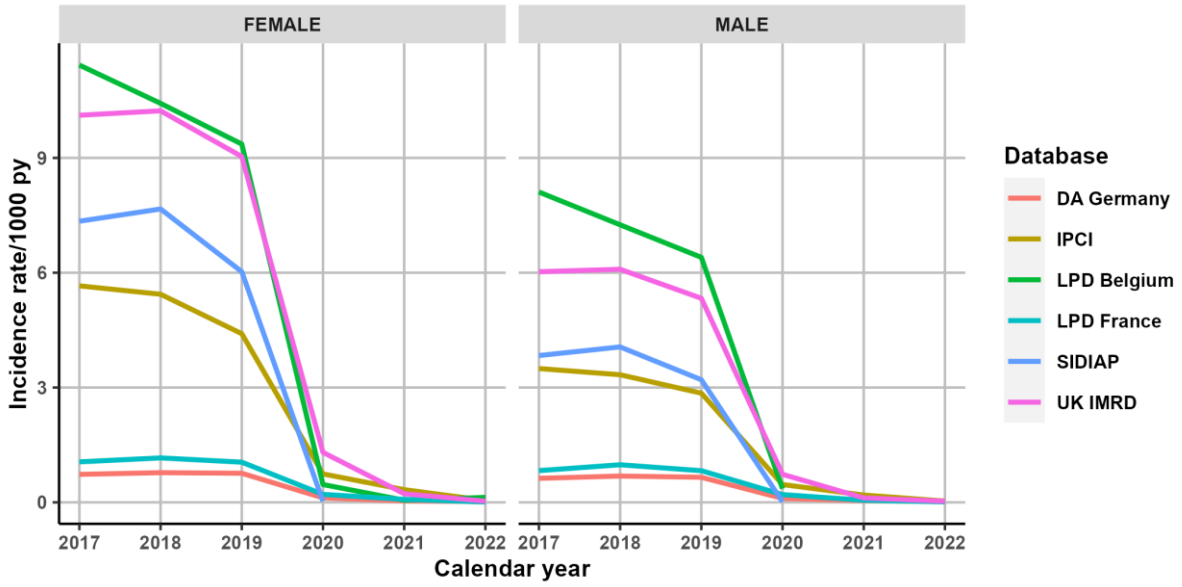

Figure 8 Incidence of ranitidine, by sex and calendar year

Incidence of ranitidine use tended to be higher in female compared to male users, especially in IMRD (UK), LPD Belgium and SIDIAP (Spain) (Figure 8 Incidence of ranitidine, by sex and calendar year).

Also for PPIs, use was the lowest in children, increased with age and was the highest from the age of 60 on and decreased again in adults older than 80 years (Appendix Figure 12). Use of PPIs was higher in female than in male users (Appendix Figure 18). Incidence of other alternative drugs (stratified by sex and age) over time is available in the appendix of the report (Appendix Figures 9-11; Figures 13-17 and Figures 19-20).

9.4 Switching to alternative medications

9.4.1 Early switching over time

Next the proportion of individuals switching from ranitidine to alternative drugs was explored. Early switching was defined as switching from ranitidine to alternative medicines within 90 days after end of ranitidine exposure.

Individuals mainly switched from ranitidine to PPIs and the incidence of switching increased with calendar time especially from 2019 on where a sharp increase was observed up to 2020 (Figure 9 Early switching). Proportion of switching to PPI ranged between 234 (SIDIAP) to 684 (IPCI) per 1,000 ranitidine users. After 2020, the proportion of individuals that switched decreased again especially in IPCI (NL), LPD Belgium and DA Germany. (Figure 9 Early switching and Appendix – Table 1) Switching to other H_2RA was also observed but this proportion was much lower and mainly observed in IMRD (UK), IPCI (NL) and to a lesser extend in DA Germany and SIDIAP (Spain). Switching to antacids was mainly observed in IPCI (NL) and IMRD (UK) but with proportions that were much lower than switching to PPIs.

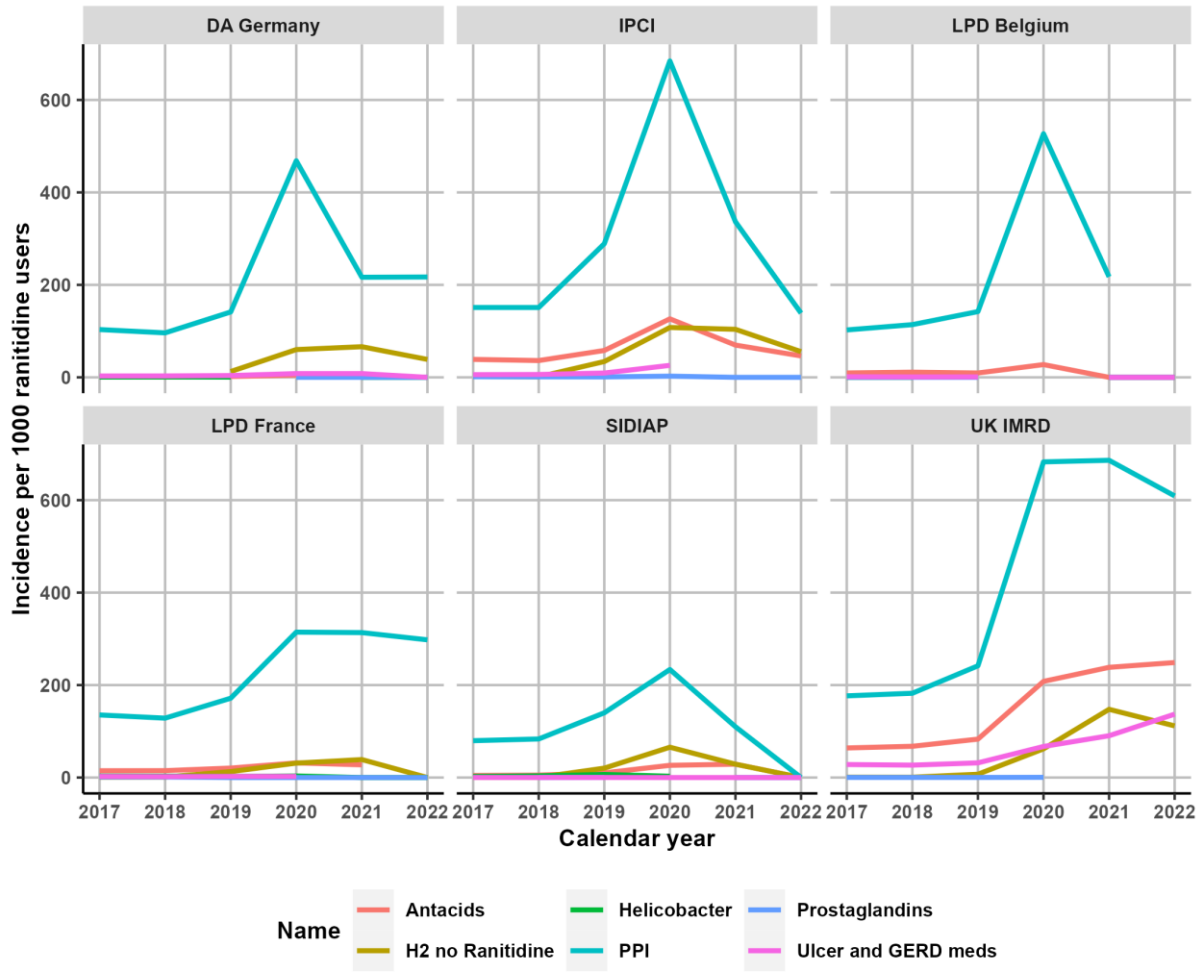

Figure 9 Early switching

Legend: Incidence rates were not provided if the numbers of individuals which switched to alternative drugs is <5.

9.4.2 Late switching

Late switching was 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. A similar pattern was observed where ranitidine users mainly switched to PPIs, but the proportion of late switching was higher than the proportion of early switching (Figure 10 Late switching) with proportions of switching to PPIs almost reaching 100% in 2021 for LPD Belgium and SIDIAP Spain. After 2020 - 2021, switching decreased or remained stable (Figure 10 Late switching and appendix – Table 2). Switching to alternative drugs, other than PPIs was observed but switching to these alternative drugs occurred in less than 30% of ranitidine users and mainly consisted of antacids, other H_2RA and other drugs for treatment of peptic ulcer or GERD.

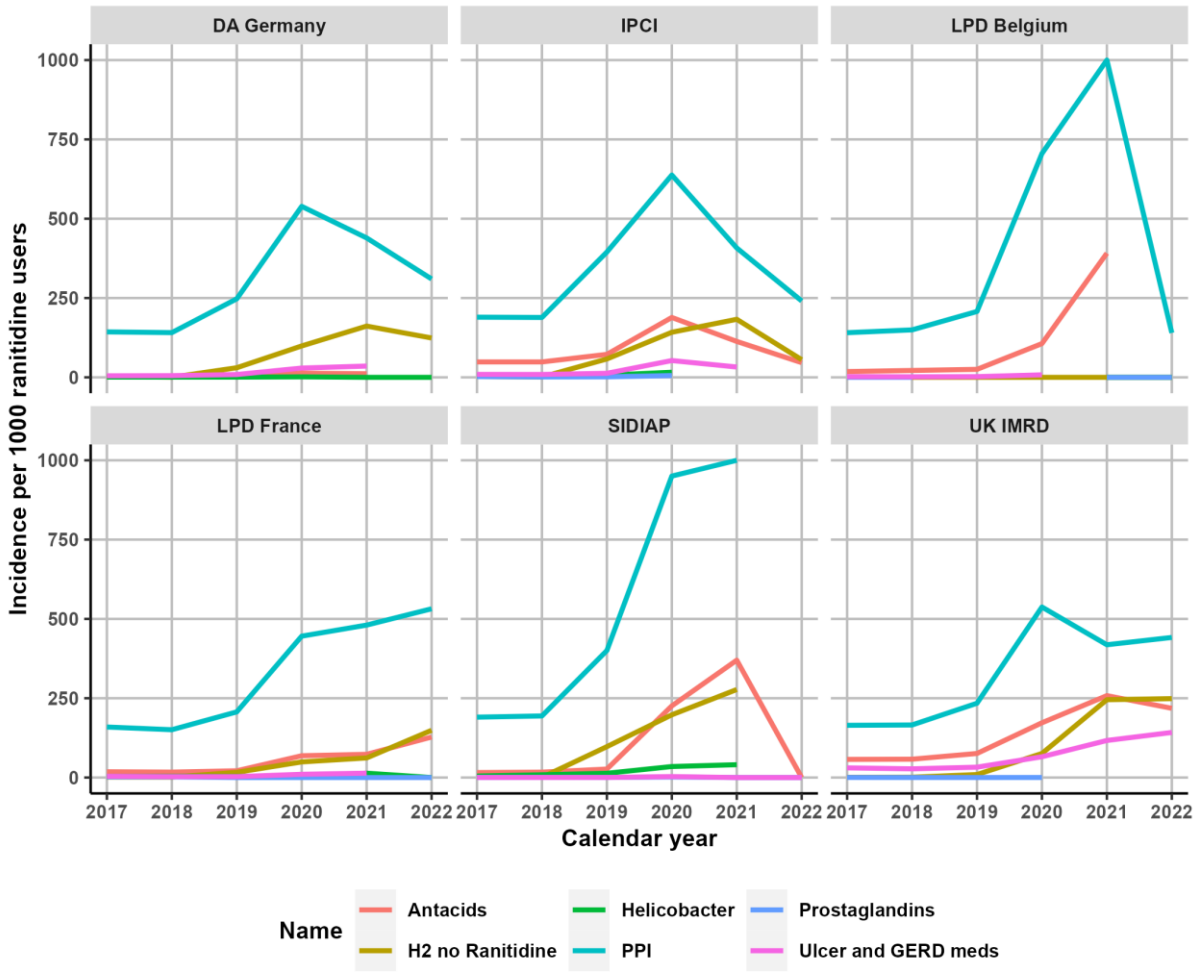

Figure 10 Late switching

Legend: Incidence rates were not provided if the numbers of individuals with switched to alternative drugs is <5.

9.5 Incidence of discontinuation in individuals treated with ranitidine

A patient was defined as discontinuing ranitidine treatment in case there was a gap of at least 90 days after the end date of the last ranitidine episode without start of an alternative medication. In addition, a sensitivity analysis was conducted investigating the incidence of patients discontinuing treatment with ranitidine for at least 365 days (i.e. “Long-Term discontinuation”).

Results of the main analysis and the sensitivity analysis are provided in Tables 12-13 of the Appendix as well as in Figure 11 Incidence of discontinuation of ranitidine use (i.e. time following last prescription of ranitidine of at least 90 days) and Figure 12 Long term discontinuation of ranitidine (i.e. time following last prescription of ranitidine of at least 365 days).

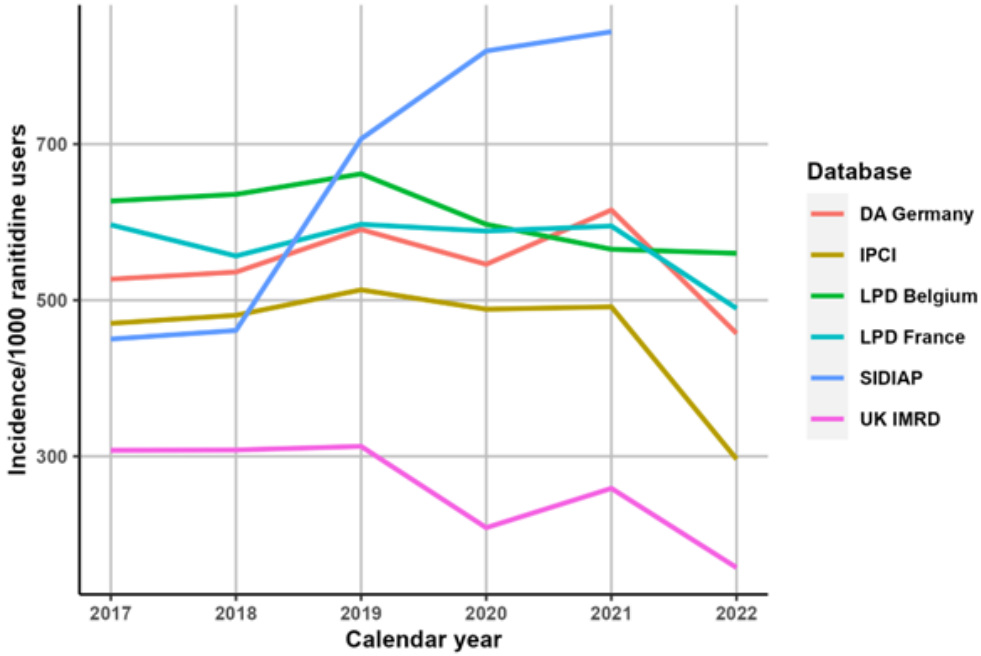

Figure 11 Incidence of discontinuation of ranitidine use (i.e. time following last prescription of ranitidine of at least 90 days)

The incidence of ranitidine users which discontinued therapy was comparable for LPD Belgium, LPD France, DA Germany and IPCI (NL) (range of 270 - 380/1,000 users at start of follow-up) whereas the incidence of ranitidine discontinuation was the lowest for IMRD (UK) (i.e., 133/1,000 users at start of follow-up) (see Appendix - Table 12). For most of the databases, the rate of discontinuation remained relatively stable over time and decreased from 2021 on (except for LPD Belgium). In SIDIAP, an import increase in the incidence of discontinuation was observed from 2018 on.

Figure 12 Long term discontinuation of ranitidine represents “long term discontinuation” of ranitidine showing that discontinuation rates start to decrease from 2019 on for all databases (and from 2021 on for SIDIAP (Spain)). Overall long-term discontinuation rates are much lower compared to the discontinuation rate defined by a gap of 90 days following end date of last ranitidine episode (see Figure 11 Incidence of discontinuation of ranitidine use (i.e. time following last prescription of ranitidine of at least 90 days).

Discontinuation rates of ranitidine by age and sex are provided in the appendix. (Appendix Figures 21-26). Whereas no important differences in discontinuation rates of ranitidine were observed by sex, discontinuation rates are higher for the younger population compared to adults and the elderly especially with regard to long term discontinuation (appendix Figures 23 and 26).

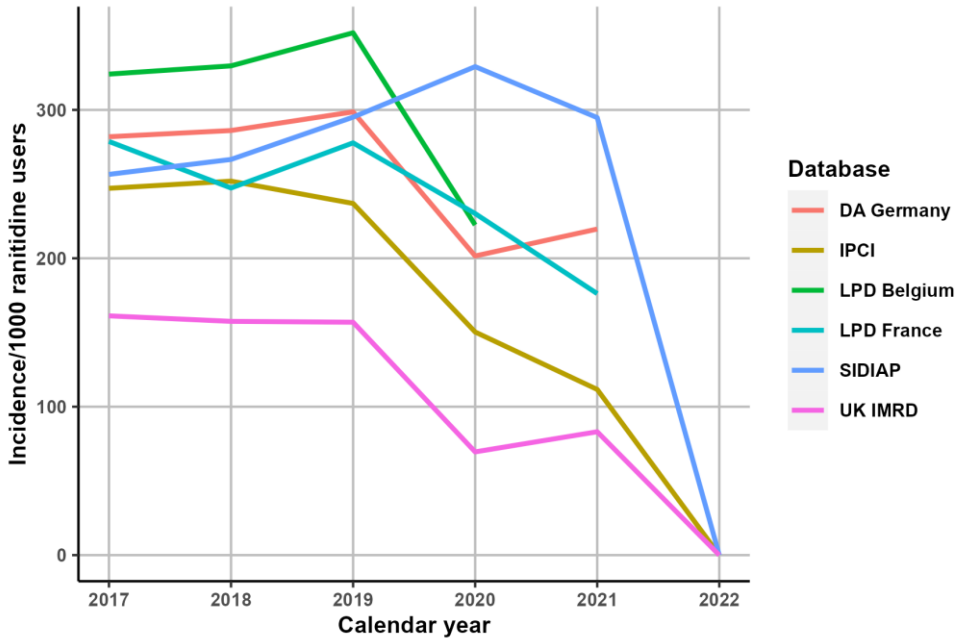

Figure 12 Long term discontinuation of ranitidine (i.e. time following last prescription of ranitidine of at least 365 days)

Legend: Incidence rates were not provided if the numbers of individuals that discontinued is <5.

9.6 Drug prescribing in individuals with an indication for use of ranitidine or alternative drugs

Next, the incidence of drug use in a cohort of individuals diagnosed with conditions for which use of ranitidine was indicated prior to suspension (i.e., group of patients diagnosed with GERD, peptic ulcer disease (w/o H. Pylori), Zollinger Ellison Syndrome, dyspepsia/indigestion) was investigated. For this calculation of the incidence rate, the numerator consisted of the number of incident users in the 180 days following the first diagnosis of interest and the denominator consisted of the person time of patients with the indication of use during the 180 days following the first diagnosis of interest.

Results are presented by calendar year (Appendix – Table 14) and by referral period (Appendix – Table 15). In all databases, in patients newly diagnosed with any of the conditions of interest, mainly PPIs were prescribed with incidence rates varying between 346/1,000 PY (IPCI) and 809/1,000 PY (LPD Belgium) at the start of the study and incidence rates of 126/1,000 PY (IPCI) to 525/1,000 PY (LPD Belgium) in 2022 (Figure 13 Incidence of PPIs prescribing in individuals newly diagnosed with conditions for which treatment with ranitidine or alternative drugs is indicated).

Initiation of H_2RA was much lower with an incidence rate of 19/1,000 PY (DA Germany) to 195/1,000 (LPD Belgium) in 2017 to an incidence of 1.9/1,000 PY (DA Germany) to 28.6/1,000 PY (IMRD UK) in 2022 (Appendix Figure 27). Similar results were observed for ranitidine (which was the most prescribed H_2RA) with incidence rates decreasing to almost 0 in 2022 (Figure 14 Incidence of ranitidine prescribing in individuals newly diagnosed with conditions for which treatment ranitidine or alternative drugs is

indicated). Use of other drugs such as antacids, prostaglandins, drugs used for the eradication of H Pylori was much lower (see Tables 14 and 15 in the appendix and Figures 28-32).

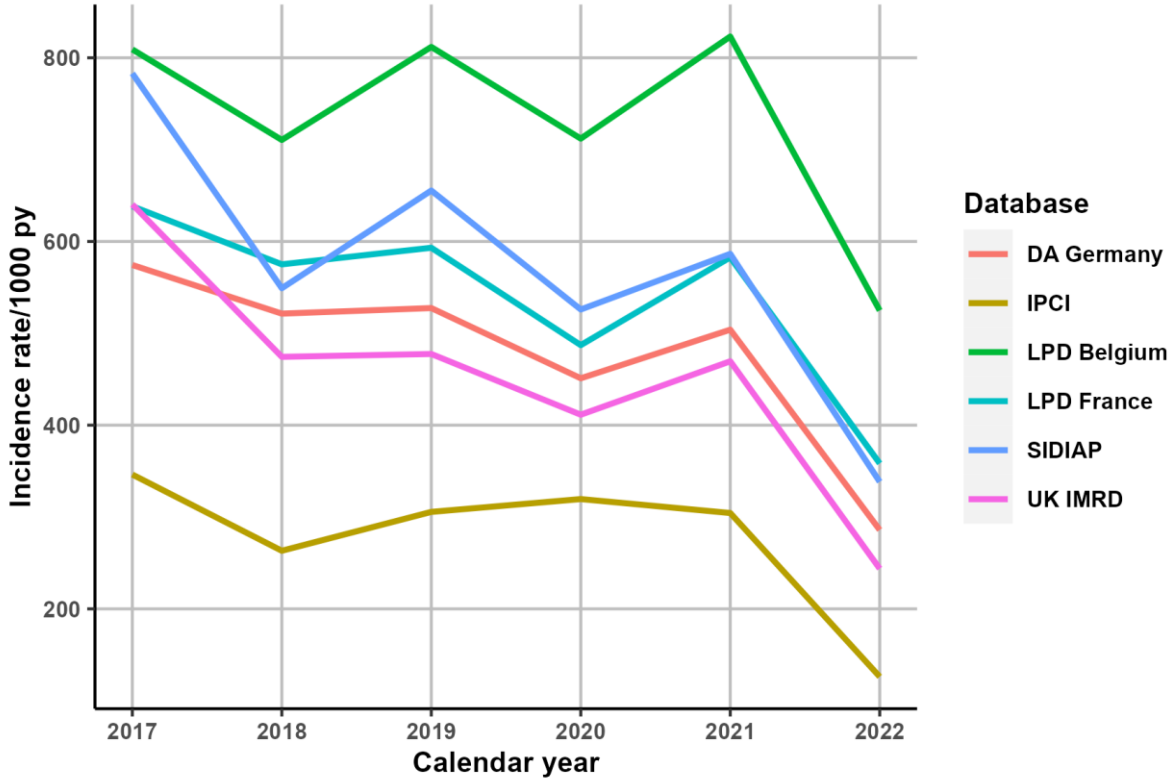

Figure 13 Incidence of PPIs prescribing in individuals newly diagnosed with conditions for which treatment with ranitidine or alternative drugs is indicated

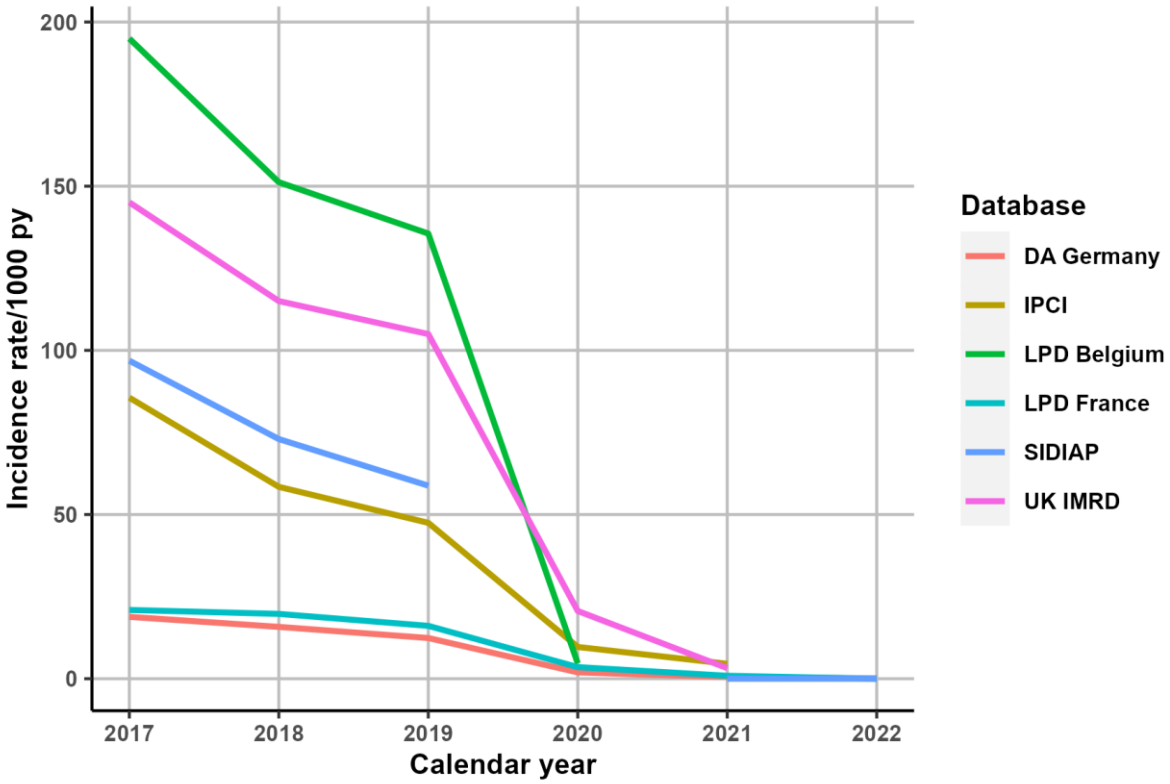

Figure 14 Incidence of ranitidine prescribing in individuals newly diagnosed with conditions for which treatment ranitidine or alternative drugs is indicated

Legend: Incidence rates were not provided if the numbers of individuals newly being prescribed ranitidine is <5.

Table 15 from the appendix describes the incidence of drug use by period in individuals newly diagnosed with any of the conditions of interest. Similar findings were observed as described above with highest use for PPIs and incidence rates of ranitidine decreasing below 10/1,000 in the post-referral period.

9.7 Time series analysis

The results of the time series analysis for the incidence of ranitidine use per quarter are presented in Figure 15 Results of time series analysis for incidence of ranitidine prescribing and in Table 9 (timing of join points).

In DA Germany, IPCI, SIDIAP and UK IMRD a steep decrease started in July 2019 and ended in October or November (UK IMRD) 2019. In Belgium and France decrease started in February 2019 and ended in January 2020 LPD Belgium) or February 2020 (LPD France).

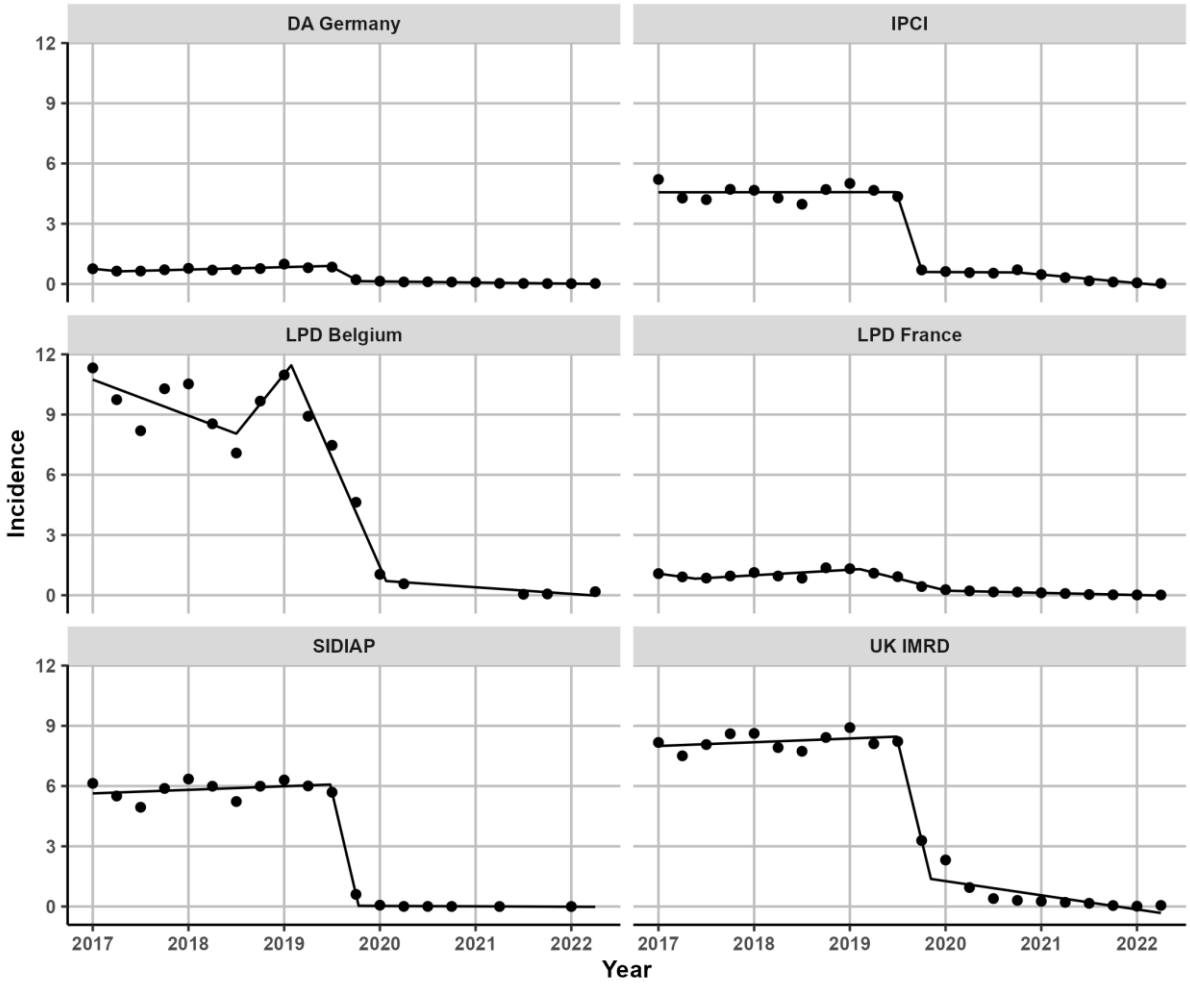

Figure 15 Results of time series analysis for incidence of ranitidine prescribing

Legend: Dots provide observed incidence per quarter; lines are predictions from the join point analysis.

DA Germany		IPCI		LPD Belgium		LPD France		SIDIAP		UK IMRD	
year	month	year	month	year	month	year	month	year	month	year	month
2017	4	2019	7	2018	7	2017	6	2019	7	2019	7
2019	7	2019	10	2019	2	2019	2	2019	10	2019	11
2019	10	2020	10	2020	2	2020	1				

Table 9 Timing of join points in time series analysis

9.8 Sensitivity analyses

As described in the method section, the planned sensitivity analyses consisted of the following:

- Extending window in which the indication of use of ranitidine is extended from 180 to 365 days.

- Long term discontinuation which was defined as patients discontinuing treatment for at least 365 days.

Results of the first sensitivity analysis are available in Table 4 of the appendix. No important differences in the proportion of indications between the different periods were observed and the indication of use of ranitidine was often missing. When extending the look-back period from 180 to 365 days, the proportion of patients with an indication of use increased (up to a factor 2) in all databases except for IPCI (NL) where this increase was only modest.

Results on the sensitivity analysis for long term discontinuation are presented in Figure 9 and Table 13 of the appendix. Overall long-term discontinuation rates were much lower (around factor 0.5 at start of the study) compared to the discontinuation rate defined by a gap of 90 days following end date of last ranitidine episode. This difference became even more pronounced at the end of the study period in all databases.

10 Discussion

10.1 Key results and interpretation

During the study period, among 45 million individuals 385,273 users of ranitidine were observed of which the majority (304,968) occurred during the pre-referral period. The number of ranitidine users decreased substantially in the in-referral and in the post-referral period.

Most ranitidine users were female for all databases and across referral periods (pre-, in- and post-referral period) and most ranitidine users were between 18-74 years. Use of ranitidine mainly consisted of oral use which coincides with the fact that primary care databases were used.

The indication of use (based on predefined definitions) was often missing (in <=15% of users of ranitidine, predefined indications of use could be identified). For those prescriptions where indication of use was available, it mainly consisted of gastritis without H Pylori or GERD.
Amongst the available H_2RA, ranitidine was most frequently prescribed with incidence rates ranging between 0.7-9.9/1000 PY in 2017. These numbers decreased almost to 0/1,000 PY in the post-referral period. Of all drugs of interest, PPIs was the drug class which was most frequently prescribed with incidence rates varying between 20.9-56.2/1,000 PY in 2017. During the in-referral period, an increase of use of PPIs was observed which stabilized or decreased during the post-referral period (April 2020 - March 2022).

The incidence of switching from ranitidine to alternative drugs increased with calendar time especially from 2019 on where a sharp increase was observed up to 2020. Individuals mainly switched from ranitidine to PPIs. After 2020, the proportion of individuals that switched decreased again, especially in IPCI (NL), LPD Belgium and DA Germany. This sharp increase in use of PPIs in the in-referral period is likely due to the fact that patients who were on treatment with ranitidine had to switch to alternative treatments. At the end of the study period there were not only very few patients remaining on ranitidine but also the number of individuals with sufficient follow-up time to define “early switching” (need of at least 90 days following last ranitidine prescription) and “late switching” (need of at least 365 days following last ranitidine prescription) became very low. This resulted in a decrease of switchers to PPI at the end of the study period but also more uncertainty because of low numbers. Switching to other H2RA was also observed but this proportion was much lower and was mainly observed in IMRD (UK), IPCI (NL) and to a lesser extend in DA Germany and SIDIAP (Spain).
The incidence of ranitidine users which discontinued therapy was comparable for LPD Belgium, LPD France, DA Germany and IPCI (NL) (range of 270 - 380/1,000 users at start of follow-up) whereas the incidence of ranitidine discontinuation was the lowest for IMRD (UK) (i.e., 133/1,000 users at start of follow-up). For most of the databases, the rate of discontinuation remained relatively stable over time and decreased as of 2021. The incidence of long-term discontinuation decreased as of 2019 for all databases except SIDIAP (Spain) where a decrease was observed as of 2021. Overall, long term

discontinuation rates are much lower compared to the discontinuation rate defined by a gap of 90 days following the end date of the last ranitidine episode.

When investigating the use of medications in individuals newly diagnosed with conditions for which use of ranitidine was indicated prior to suspension, mainly PPIs were prescribed with incidence rates varying between 346/1,000 PY - 809/1,000 PY at the start of the study and incidence rates of 126/1,000 PY - 525/1,000 PY in 2022. Initiation of H_2RA was much lower with an incidence rate of 19/1,000 PY - 195/1,000 PY in 2017 to an incidence of 1.9/1,000 PY - 28.6/1,000 PY in 2022. Similar results were observed for ranitidine (which was the most prescribed H_2RA) with incidence rates decreasing to almost 0 in 2022.

The results from the time series analysis reported a steep decrease in incidence of ranitidine prescribing which started in July 2019 for DA Germany, IPCI (NL) and IMRD (UK) while for LPD Belgium and LPD France this decrease started in February 2019.

In our study, we not only observed a decrease in prescribing of ranitidine but also reported that patients mainly switched from ranitidine to PPIs. So far, there are few studies describing use patterns of ranitidine and other H_2RA. Other research groups also reported a decrease of H_2RA in favour of PPIs as these are considered more effective than H_2RA in both preventing and healing ulcers. (3).

Few studies allowed us to compare our data to the results of others. Kurdi et al. used Scottish claims data between 2001 to 2017 to investigate utilisation and prescribing patterns of PPIs. They reported an increase of use PPIs over time from 1.8 million items dispensed in 2001 to 5.5 million items in 2017. The authors contributed these findings to various factors amongst one is the evidence from RCTs on a higher efficacy of PPIs vs H_2RAs in preventing as well as healing ulcers resulting in a lower prevalence of H_2RAs use.(3). Martin et al. investigated trends in prescribing PPIs and H_2RAs in primary care by means of a postal survey sent to 250 primary care physicians in the UK during the study period 1991-1996. They not only reported a sharp increase in the use of PPIs at the expense of H_2RAs, but they also described that H_2RAs were more often discontinued compared to PPIs because of treatment failure.(4) A study in Iceland described the real-world use of PPIs during 2003-2015 and reported an incidence of 3.3 - 4.1 per 100 persons per year. Although we investigated a different study period, the incidence rates of PPIs that we reported were in line with the results Icelandic study where we reported incidence rates of PPIs prescribing ranging between 20.9 - 56.2/1000 PY in 2017. (2)

Some switching from ranitidine to other H_2RAs was observed, but this proportion was low (less than 20% for early switchers) and was mainly observed in IMRD (UK), IPCI (NL) and to a lesser extend in DA Germany and SIDIAP (Spain). This low proportion can be explained by the fact that very few alternative H_2RAs other than ranitidine are still available in the EU. For instance, in Belgium, there are no alternative H_2RAs available, which is a concern for patients requiring a pre-medication regimen intended to reduce the risk of hypersensitivity reactions to a variety of chemotherapy agents. (17) A recent study using data from the English Prescribing Dataset investigated the effect of COVID-19 on

primary care prescribing. Following the suspension of ranitidine, the authors reported a decrease by 99.6% in August 2020. This was offset by an increase in famotidine and cimetidine. (1)

In patients diagnosed with a condition for which ranitidine or alternative drugs were indicated, PPIs were mainly prescribed where during the in-referral period, an increase of use of PPIs was observed which stabilized or decreased during the post-referral period (April 2020 - March 2022). These results could have been affected by the SARS-CoV-2 pandemic ("COVID") which coincided with the study period. While the incident of new PPI users initially increases following the referral this trend flattens out or slightly decrease, potentially indicating an effect of the pandemic situation. Indeed, during the pandemic, for certain individuals it was difficult to get access to regular health care. (18) Also, initially some literature reported on poor outcome in patients with Covid-19 treated with PPIs, however this association could no longer be confirmed in recent research. (19, 20)

10.2 Limitations

For this study, real-world data from electronic healthcare records was used. There might be differences between the databases regarding availability of certain data. First, conditions which determine the indication of use of ranitidine and alternative drugs might not be available in the source databases. This is also what was observed as the indication of use was missing in up to 85% of the population (this proportion decreased to 75% when extending the look-back period to one year). It is likely to assume that the exact indication of use of ranitidine or alternative drugs is based on endoscopy results (thus done by the specialist) which might not always be coded by the GP in the patient's medical file. Also, there is the potential that the predefined concepts for the different indications of use (e.g. gastric ulcer w/wo H. Pylori, duodenal ulcer w/wo H. Pylori, etc.) which we had defined at time of protocol generation and analysis do not contain all existing disease codes as used by the different data sources. Because of this limitation, we also investigated disease codes entered within the patient's medical file at time of prescribing. When exploring all potential disease codes within 14 days prior to the index date, it is clear that ranitidine (and alternative drugs) were prescribed for reason of gastro-intestinal complaints.

Second, there is the potential of underreporting of ranitidine use as well as use of alternatives for those drugs, which are also available as over the counter (OTC) drugs, (e.g., antacids and low dose H_2RAs as well as PPIs). In contrast, as prescription and dispensing data were used, we might overestimate the use of ranitidine and other H_2RAs as the actual drug intake might have been lower. Third, as primary care databases were used, use of H_2RAs and alternative drugs in the hospital setting is lacking. And finally, there might be missing information in some of the databases for instance in LPD France where information on dosing was missing and type of formulation not available for all users of ranitidine in UK IMRD, IPCI and LPD France.

10.3 Strengths and Generalisability

Generalisability of our findings is high as we used real-world data to investigate treatment patterns of ranitidine and alternative drugs. The strength of our study is the fact that we used large datasets from multiple countries with source data mapped to the OMOP common data model, which allowed us to

optimize our research and obtain the data in a fast and efficient way. Also, results are not only presented in this report and in the ancillary tables, but all results can be accessed via the web application. Although there are some country specific differences in the results there are numerous consistent findings regarding the characteristics of ranitidine users but also regarding trends in incidence rates with decreasing trends of ranitidine use during the study period with an increase of PPI use in the in-referral period which stabilized or decreased again in the post-referral period.

11 Other information

Not applicable

12 Conclusions

In this study, we report a decrease of ranitidine use during the study period with incidence rates almost decreasing to 0 in the post-referral period. Of potential alternative drugs to ranitidine, use of PPIs was the highest and use increased during the in-referral period but either stabilized or decreased during the post-referral period depending on the database being investigated. The incidence of switching from ranitidine to alternative drugs increased with calendar time especially from 2019 on. Individuals mainly switched from ranitidine to PPIs. After 2020, the proportion of individuals that switched decreased again, especially in IPCI (NL), LPD Belgium and DA Germany. In patients newly diagnosed with conditions for which use of ranitidine or alternative drugs was indicated, mainly treatment with PPIs was initiated whereas initiation of H_2RAs was much lower.

13 References

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14 Addendum 1

14.1 List of ATC codes

ATC code	Description
H2 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,
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
A02BX	Other drugs for peptic ulcer and gastro-

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

14.2 Indication of use - 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
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

concept_id	concept_name	concept_code	With H Pylori
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

concept_id	concept_name	concept_code	With H Pylori
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
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

concept_id	concept_name	concept_code	With H Pylori
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

concept_id	concept_name	concept_code	With H Pylori
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
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

concept_id	concept_name	concept_code	With H Pylori
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	849601000000109	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

concept_id	concept_name	concept_code	With H Pylori
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
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

concept_id	concept_name	concept_code	With H Pylori
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
440755	Acute duodenal ulcer without hemorrhage, without perforation AND without obstruction	23693000	No
434402	Acute duodenal ulcer with hemorrhage but without obstruction	66767006	No

concept_id	concept_name	concept_code	With H Pylori
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

concept_id	concept_name	concept_code
40317098	Hyperacidity	155722007
40325737	Gastric irritation	162027003

14.3 DDD of H2-receptor antagonist ingredients

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