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

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Research question and objectives	Ranitidine is a competitive and reversible inhibitor of the action of histamine and indicated for the management of peptic ulceration, Gastro-Esophageal Reflux Disease (GERD), reflux oesophagitis and Zollinger-Ellison syndrome. Results of a preliminary laboratory analysis have shown the presence of N-Nitrosodimethylamine (NDMA), a human carcinogen, in ranitidine. With this drug utilisation study, we aim to determine drug utilisation and prescription patterns of medicinal products containing H_2-receptor antagonists. These data will give insight on the number of patients using ranitidine and thus potentially at risk of NDMA. In particular we will: 1. Study the prevalence and incidence prescribing of H_2-receptor antagonists as a class and by individual drug 2. Explore the characteristics of H_2-receptor antagonist use with regard to age (10-years age

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

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

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1 List of abbreviations

Abbreviation	Name
ATC	Anatomical Therapeutic Chemical Classification
CDM	Common Data Model
CHMP	Committee for Medicinal Products for Human Use
DDD	Defined Daily Dose
DUS	Drug Utilisation Study
EHR	Electronic Healthcare Record
ETL	Extract Transform Load
GERD	Gastro-oesophageal reflux disease
GP	General practitioner
H_2	Histamine 2
H_2RA	Histamine 2 receptor antagonist
IQR	Interquartile range
NAP	Not applicable
NDMA	N-Nitrosodimethylamine
OTC	Over The Counter
PDD	Prescribed Daily Dose
Q1	First Quartile
Q3	Third Quartile

2 Abstract

Title

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

Version and Date: 7th April 2020 – Final Study Report
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Keywords

H_2-receptor antagonists, ranitidine, drug utilisation

Rationale and background

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

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

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

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

Research question and objectives

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

Study design

Retrospective cohort study using electronic healthcare records from six databases from six European countries: Belgium (LPD Belgium), the Netherlands (IPCI), Germany (DA Germany), France (DA

France), UK (IMRD) and Spain (SIDIAP). All these databases have their data mapped to the OMOP Common Data Model.

Subjects and study size

The study population consisted of all persons with observation time during the study period (1992-2020). These were in total 41,947,608 individuals (7,079,130 in DA_France, 10,735,745 in DA Germany, 12,724,481 in IMRD, 2,499,976 in IPCI, 1,145,962 in LPD_Belgium, and 7,762,314 in SIDIAP).

Variables

Number of users of H_2-receptor antagonists (H_2RA) and individual H_2RA, was investigated by calculating prevalent (number of users per 1,000 persons) and incident use (number of new users per 1,000 persons). Exposure was categorized by sex, age group and calendar year.

The cumulative exposure to H_2RA, ranitidine and other H_2RA was investigated by calculating the cumulative duration of use – which was the sum of the duration of the individual treatment episodes. Next, information on exposure in dose was assessed and consisted of the calculation of the PDD (Prescribed Daily Dose)/DDD (Defined Daily Dose) ratio, the cumulative dose (in mg and DDD) and the cumulative annual dose (mg/PY). The cumulative duration was categorised according to the ICH M7 categories into ≤1 month, >1-12 months, >1-10 years, > 10 years. The cumulative exposure in days and mg was also investigated by type of formulation (oral or parenteral)

For all patients exposed to H_2RA during follow-up we investigated the indication of use in the one year prior to the first prescription. The indication of use was the following: GERD, Zollinger Ellison syndrome, gastric/duodenal ulcer. Also, the presence of chronic renal impairment was investigated by checking for disease codes of chronic renal impairment in the one year prior to the first prescription.

Results

The total number of users of H_2RA use was 1,135,717 (36,826 in DA France, 170,600 in DA Germany, 714,828 in IMDR, 63,594 in IPCI, 53,206 in LPD Belgium and 96,663 in SIDIAP). The number of users of ranitidine was 1,006,319 (31,613 in DA_France, 150,513 in DA Germany, 615,485 in IMDR, 61,063 in IPCI, 52,683 in LPD Belgium and 94,962 in SIDIAP).

The incidence of H_2RA, assessed per database in each available calendar year, was lowest (0.7/1,000) in SIDIAP in 2017 and highest (13.2/1,000) in IPCI in 1997. Similar results were observed for the incidence of ranitidine with a range from 0.7/1,000 (SIDIAP in 2007) to 11.4/1,000 (LPD_Belgium in 2012). The incidence of ranitidine (and other H_2RA) was higher in females than in males and decreased over calendar time in DA_Germany, IPCI and LPD_Belgium but in all databases remained stable over the last 5 years (2014-2019). The prevalence of ranitidine ranged between 1.0/1,000 (SIDIAP in 2006) and 28.3/1,000 (LPD_Belgium in 2010). Similar findings regarding change over calendar time and difference by gender were observed as for the incidence of ranitidine. In all databases, use increased with age from the age of 20 years on and was the highest in patients aged 70-90 years.

Mainly ranitidine via oral formulation was prescribed and/or dispensed. Use of parenteral ranitidine was less than 2% of all ranitidine users in all databases.

With regard to the other type of H_2RA, mainly cimetidine was used but with lower prevalences and incidences than ranitidine and use dropped almost to 0 over calendar time. The use of the other H_2RA (Famotidine, Nizatidine, Roxatidine, Ranitidine bismuth) was low or non-existing.

The proportion of patients using ranitidine for a duration between 1-10 years, considering the total study period, was low and ranged between 6.5-18.8% (DA_France and IMRD respectively). Use of ranitidine for more than 10 years ranged between 0.03-3.3% (DA_Germany and SIDIAP respectively).

The median cumulative duration of ranitidine ranged between 28 days (P5-P95=7-480) in DA_France to 60 in IMRD (P5-P95=15-1,800). In all databases, the median cumulative duration of ranitidine was highest in patients >75 years.

The median cumulative DDD of ranitidine, assessed for each patient over the total study period, ranged between 28 (DA_Germany) and 56 (IMRD) DDD. No differences with gender was observed but, in all databases, the median cumulative DDD was the lowest in the youngest age categories and highest in patients older than 75 years. The median cumulative DDD was also lower for parenteral use compared to oral use and comparable irrespective of the indication of use.

Similar results were observed when investigating cumulative dose in gram, assessed for each patient over the total study period, with – for ranitidine – a median cumulative dose ranging between 8.4 (DA_France) and 16.8 (IMRD) gram. The median cumulative annual dose of ranitidine in gram per year ranged between 1.5 g (DA_Germany) and 2.3 g (LPD Belgium and DA_France). The median cumulative annual dose was lowest in children < 18 years, increased with age and was the highest in individuals older than 75 years.

In all databases, the median PDD/DDD ratio for ranitidine was around 1 implying that the patient was prescribed ranitidine in agreement with the dose recommendations from the WHO. In children and for parenteral use, lower median PDD/DDD ratios were observed.

The indication of use (assessed by presence of a disease code in the year prior to the first H_2RA exposure) was often missing. Of the patients with an indication of use, the majority used ranitidine for reflux disease (range over databases 71-94%).

In all databases, the percentage of patients with renal impairment within the users of H_2RA was less than 2%.

Discussion

In this study we report a low use of ranitidine (and other H_2RA) with a decrease over calendar time which was mainly obvious in DA_Germany, IPCI and LPD_Belgium. In all databases, use stabilized over the last 5 years. Our findings are in line with results from other research groups also reporting a decrease in use of H_2RA in favor of proton pump inhibitors.

Less than 1 patient in 5 used ranitidine for a cumulative duration between 1-10 years and less than 4% of patients used ranitidine for more than 10 years which is in line with the Summary of Product Characteristics (SPC) of ranitidine that only recommends maintenance therapy with ranitidine for strict indications.

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. Similarly, also the proportion of patients with chronic kidney injury was underestimated. Also, not all information on dosing was available and OTC use of H_2RA as well as use of H_2RA in secondary care was missing. Our main strength is the fact that we used real life data on a large dataset from multiple countries with source data mapped to the OMOP common data model. This methodology allowed us to optimize our research and 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 consulted in the web application.

Conclusion

Amongst the H_2RA, mainly ranitidine was used but with low incidence numbers (less than 3% initiate treatment in one follow-up year) and country specific differences. Less than 3% of patients are treated with ranitidine with the highest use in females and in the elderly. A decrease in incidence and prevalence over calendar time has been observed, although not in all databases, but use has been stabilized over the past 5 years.

The proportion of patients using ranitidine for more than 10 years was less than 5% of all ranitidine users implying that the median cumulative duration and median cumulative exposure is low.

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4 Milestones

Milestone	Planned Date	Actual Date
Approval Study Protocol by EMA	17th January 2020	17th January 2020
Registration in the EU PAS register	31st January 2020	2nd February 2020
Start of data collection	Not applicable – EHR databases will be used where all data has already been collected	
End of data collection	Not applicable – EHR databases will be used where all data has already been collected	
Draft report	13th March 2020	13th March 2020
Final study report accepted by EMA	27th March 2020	7th April 2020
Manuscript to be provided to EMA	29th May 2020	

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

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

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

To answer these questions, the EMA launched an invitation to tender under Lot 3 – Rapid Descriptive Studies. This drug utilisation study (DUS) was conducted as part of this tender.

6 Research question and objectives

This study explores real-world use of ranitidine and other H_2 antagonists and in particular:

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

7 Amendments and updates to the protocol

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

No amendments of the protocol were made

8 Research methods

8.1. Study design

A retrospective cohort study was conducted using electronic healthcare records from six databases from six European countries: Belgium (LPD Belgium), the Netherlands (IPCI), Germany (DA Germany), France (DA France), UK (IMRD) and Spain (SIDIAP).

8.2. Setting

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

For more detailed information on the individual databases, see Section 8.4 'Data sources'.

Study population

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

Study period

The study period started at the first available date in the databases (1992) and ended at the last data cut-off (2019).

Inclusion and exclusion criteria

As described in "Study population", subjects were included in the study if they contributed active follow-up time during the study period. No other inclusion or exclusion criteria were applied.

Follow-up

For all subjects, follow-up started at the date on which they contributed active follow-up time (= start of observation period) and follow-up ended at the end of the observation period.

8.3. Variables

Drug Exposure

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

Prevalent and incident use of H2-receptor antagonists

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

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

between H_2-receptor antagonists, this person might show up as new user of a certain ingredient but be a prevalent user of the class.

Duration of use of H2-receptor antagonists

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

Drug Exposure Duration

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

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

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

Cumulative exposure duration

Next, from the individual drug exposures, the cumulative exposure duration was calculated as the sum of the durations of the individual drug exposures of a person NOT taking into account gaps between exposures.

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

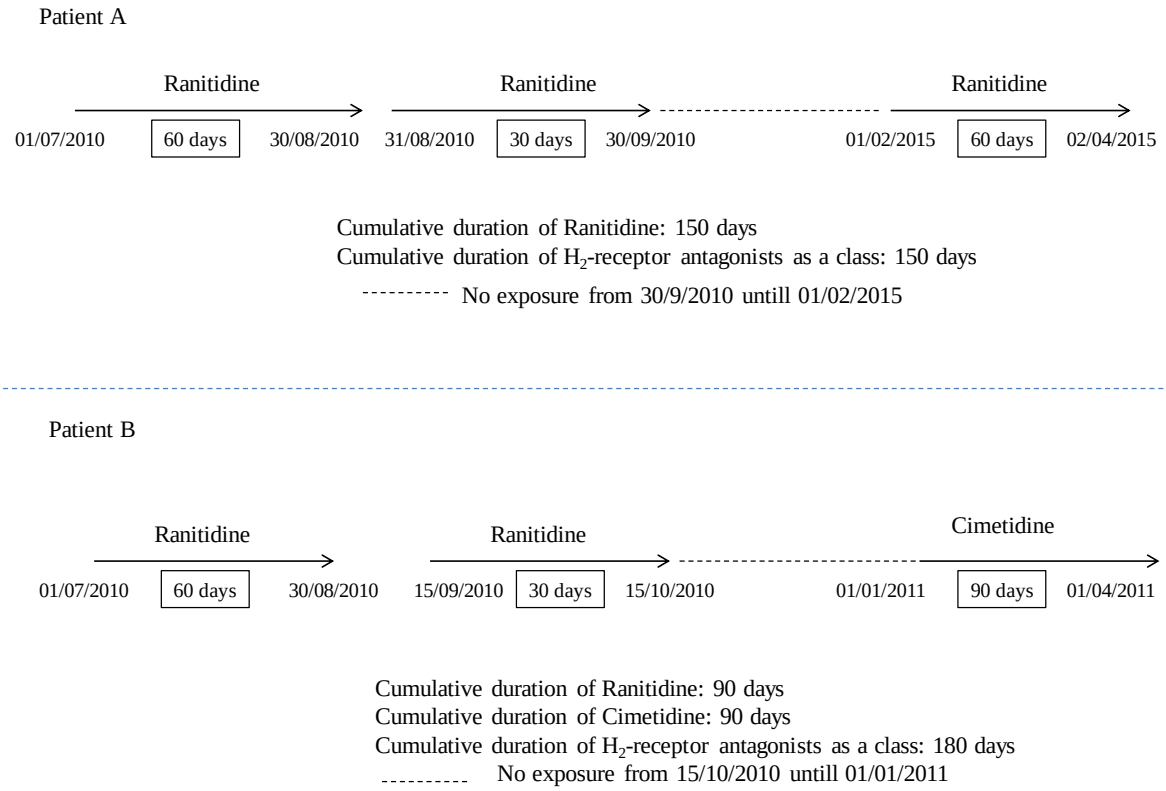

Figure 1: Calculation of cumulative duration

Dose of H2-receptor antagonists

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

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

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

Calculation of PDD

The PDD was calculated for each drug exposure. Similarly to the duration, there are different ways how the PDD can be derived from records in the DRUG_EXPOSURE table and the dose information of the DRUG_STRENGTH table (Annex 3), depending on available data:

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

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

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

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

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

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

The availability of the data elements (quantity, etc.) is reported for each of the drugs of interest in each data source.

Calculation of cumulative dose and cumulative annual dose

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

In this report, the cumulative dose is only be provided by ingredient level and not by treatment class as this is not informative.

Cumulative dose in mg

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

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

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

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

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

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

$$\text{Cumulative dose}_{\text{liquid}}[\text{mg}] = \sum_{exposures} \frac{volume\ per\ day \times numerator\_value}{denominator\_value}\ [mg] \times duration$$

Cumulative number of DDDs

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

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

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

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

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

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

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

Cumulative annual dose

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

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

The observation time started at the date on which a person contributed active follow-up time and ended at the end of the observation period.
The availability of the data elements for each of the drugs of interest is reported for each data source.

Figure 2 describes the calculation of the cumulative dose.

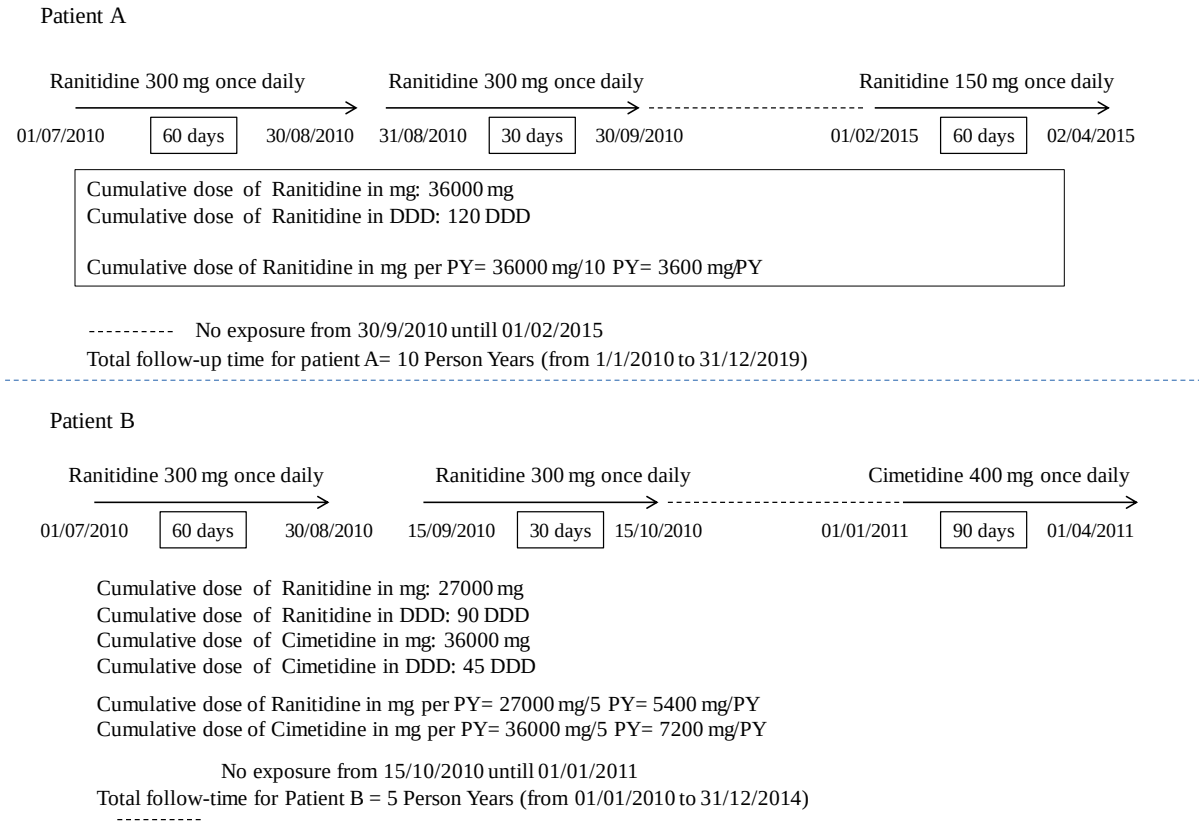

Figure 2: Calculation of cumulative dose

Figure 2 describes the use of H_2 receptor antagonists in two individual patients. Patient A received 3 prescriptions for ranitidine. The total cumulative exposure dose is 36,000 mg resulting in a cumulative number of DDDs of 120. The cumulative annual dose of ranitidine for this patient is 3,600 mg per year as this patient has 10 years of follow-up.

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

Covariates

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

Furthermore, the indication of use of H_2-receptor antagonists and the presence of renal impairment in patients exposed to ranitidine are described.

<u>Indication of use of H2-receptor antagonists</u>

The indication of use of H_2-receptor antagonist (for class as a whole, by individual ingredient and by type of formulation (oral or parenteral)) was investigated by checking the presence of conditions prior to the first prescription. Two periods to assess the presence of these conditions were used: 6 months (180 days) as well as 12 months (365 days) before of the first prescription during follow-up.

As indications were considered GERD, gastric or duodenal ulcer (with or without H Pylori), Zollinger Ellison Syndrome and unknown indication. The concept sets used for these conditions are available in Annex 4.

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

The presence of chronic renal impairment in patients using H_2-receptor antagonists was investigated by checking the presence of condition concepts in 12 months (365 days) prior to the first H_2-receptor antagonist prescription. The concept set used for this condition is available in Annex 4.

8.4. Data sources

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

IPCI – The Netherlands

Integrated Primary Care Information (IPCI), Erasmus University

IPCI is collected from EHR records of patients registered with their General Practitioner (GP) throughout the Netherlands. The selection of 391 GPs is representative of the entire country. The database contains records from 2.5 million patients out of a Dutch population of 17M (14.7%) starting in 1996. The median follow-up is 2.2 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. The duration of the drug exposure is determined for all drugs in the database by: 1. The amount and dose extracted from the sig or if instruction is “see product instructions” we use the DDD and quantity; 2. Duration available in the record; 3. If option 1 and 2 is not possible we use the DDD derived duration, use the modal duration or default to 30 days dependent on the drug of interest. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board. (Vlug, van der Lei et al. 1999)

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

SIDIAP is also collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.5M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. For the prescription records the duration is available directly from the EHR system, for dispensing the duration is inferred using the quantity, dosage, and DDD of each drug. Indication diagnoses are available from GP or hospital admission records. Drugs

not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee. (Garcia-Gil Mdel, Hermosilla et al. 2011)

Longitudinal Patient Database (LPD) Belgium (IQVIA)

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

Disease Analyser (DA) Germany (IQVIA).

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes more than 38.7M distinct person records out of at total population of 80M (48.4%) in the country, and collected from 2,734 providers. Patient visiting more than one provider are not cross-identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynecology, 6.2% various Neurology and Psychiatry 7.0% Pediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products containing information about package size, of which 92% have strength information. 24.9% also contain information about explicit duration. No registration or approval is required for drug utilization studies.

Disease Analyser (DA) France (IQVIA).

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

IMRD – UK (IQVIA)

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

98.7% of the records. Drug strength is known in 69%. All protocols have to be submitted to an independent Scientific Review Committee prior to study conduct.

8.5. Data management

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

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

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

8.6. Data analysis

All results are presented by database. Categorical data (numbers and percentages) are pooled over the different databases. For continuous variables, which all have severely skewed distrubutions, no pooling could be done as the pooled individual data is not available.

Results are shown for the treatment class of H_2-receptor antagonists as well as by ingredient.

In the Drug Utilisation R package, the following analyses were implemented:

- Drug use, both for prevalent and incident users, expressed as the number of users per 1,000 persons presented by calendar year, gender and age category.
- The cumulative duration (in days), described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, as well as the number of individuals within the ICH M7 exposure strata (duration ≤ 1 month, >1-12 months, >1-<= 10 years and > 10 years) presented by gender, age category, formulation and indication.
- In addition, the cumulative duration of drug exposure (in days), described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum for each indication and each formulation by ICH M7 drug exposure strata, age category and gender.
- The PDD/DDD ratio of the first exposure, described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, as well as the number of individuals within different strata of PDD/DDD ratio (PDD/DDD ratio < 1, PDD/DDD ratio = 1 and PDD/DDD ratio > 1), by gender, age category, formulation and indication.
- In addition, the PDD/DDD ratio, described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, for each indication and each formulation by ICH M7 drug exposure strata, age category and gender.
- The cumulative number of DDDs, described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, by gender, age category, formulation and indication.

- In addition, the cumulative number of DDDs, described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, for each indication and each formulation by ICH M7 drug exposure strata, age category and gender.

- The cumulative dose in mg, described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, by gender, age category, formulation and indication.

- In addition, the cumulative dose in mg, described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, for each indication and each formulation by ICH M7 drug exposure strata, age category and gender.

- The cumulative annual dose over the whole study period in mg/year , described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, by gender, age category, formulation and indication.

- In addition, the cumulative annual dose over the whole study , described with mean, median, 5, 25, 75 and 95 percentiles, minimum and maximum, for each indication and each formulation by ICH M7 drug exposure strata, age category and gender.

- The frequencies and proportions for indication of use, by formulation, age category and sex, presented by database as well as pooled over the databasesPatients might have more than one indication for the use of H_2-receptor antagonists e.g. use for both Zollinger Ellison and gastric ulcer thus indication of use is not mutually exclusive. The number of patients having more than one indication will be provided by database.
- The frequencies and proportions for chronic renal impairment, presented by database as well as pooled over the databases.

Indication of use was determined by the presence of conditions in two periods before the start of the drug exposure, namely 180 and 365 days before the first prescription. Determination using a look-back of 180 days was regarded as the main method and this categorisation was used in all tables. It was checked whether using a look-back of 365 days causes a change in the percentage of patients with “indication of use” of more than 25%. While this was not the case, no additional tables using the 365 look-back period are provided.

To prevent the identification of individuals, cells containing number of persons 1-5 were suppressed.

The distribution of the observation time is presented by means of a histogram.

Study results are also available in an interactive web application.

Handling of missing data

Persons with missing gender or age were not included in the study population.

If no conditions were found (in look-back periods of 180 days or 360 days, see above) to determine indication of use, this was reported as ‘unknown indication’.

Information on dosing as well as type of formulation was only provided if available. If missing, these were excluded from the denominator when calculating percentages.

9 Protection of human subjects

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

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

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

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

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

Regulatory and ethical compliance

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

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct'. (Gini, Fournie et al. 2019). The study was registered in the EU-PAS register on the 2nd February 2020.

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

10 Results

In the following sections, we focus on the main findings of this study and present the data as total numbers, median and Q1-Q3 by age category, formulation and indication of use. Data are further illustrated by graphs where needed.

The appendix contains all data on use of H_2 receptor antagonists (H_2RA), ranitidine and other H_2RA (cimetidine, famotidine, nizatidine, roxatidine, ranitidine bismuth) by database. Within the databases, there was no use of lafutidine and niperotidine during follow-up. The results are presented as total, mean, median, Q1, Q3, P5, P95, min, max, ICH category of duration of exposure. Data are presented by gender, 10-year age categories, additional age category, formulation and indication. All results (tables and figures) can also be consulted using the web application which has been created for this project (https://mi-erasmusmc.shinyapps.io/ResultsExplorer/)

10.1. Number of patients during study period

Table 1 describes the total number of patients with at least one day of observation time during the study period. For this study, we investigated use of H_2RA in more than 41 million patients during the study period 1989-2020.

Table 1 Number of patients with observation time, by database

	DA_ France	DA_ Germany	IMRD	IPCI	LPD_ Belgium	SIDIAP	Pooled
Country	France	Germany	UK	The Netherlands	Belgium	Spain	
Study period	2009 - 2020	1992 - 2020	1994 - 2019	1996 - 2018	1989 - 2020	2006-2018	1989-2020
Number of patients	7,079,130	10,735,745	12,724,481	2,499,976	1,145,962	7,762,314	41,947,608

The total number of users of H_2RA was 1,135,717 (36,826 in DA France, 170,600 in DA Germany, 714,828 in IMDR, 63,594 in IPCI, 53,206 in LPD Belgium and 96,663 in SIDIAP). The number of users of ranitidine was 1,006,319 (31,613 in DA_France, 150,513 in DA Germany, 615,485 in IMDR, 61,063 in IPCI, 52,683 in LPD Belgium and 94,962 in SIDIAP).

From these numbers, the incidence and prevalence of H_2RA by class and by individual drug was calculated and described in the following sections.

10.2. Incidence and prevalence of use of H_2RA (by class and by individual drug)

Incident use of H_2RA (by class and by individual drug)

The incidence of H_2RA over calendar time is presented in figure 3. The highest incidence (expressed as the number of new users of H_2RA/1000 persons) was reported for IPCI (13.2/1,000 (in 1997)), followed by LPD_Belgium (11.5/1,000 (in 2011)), DA_Germany (10.6/1,000 (in 1994)), IMRD (10.0/1,000 (in 1998)) and SIDIAP (2.0/1,000 (in 2018)). H_2RA use was the lowest in DA_France with rates ranging between 1.0/1,000 (2014 (lowest)) to 1.4/1,000 (2011 (highest)) . In DA_Germany, IPCI and LPD_Belgium, the incidence decreased with calendar year whereas it remained stable for IMRD and SIDIAP. Interpretation of the incidence at the start of follow-up (IMRD) and the end of follow-up (DA_France, LPD_Belgium and IMRD) is hampered because of low numbers. When use was further explored by gender, it is clear that the incidence of H_2RA use is higher in females than in males especially for IMRD, IPCI, and LPD_Belgium.

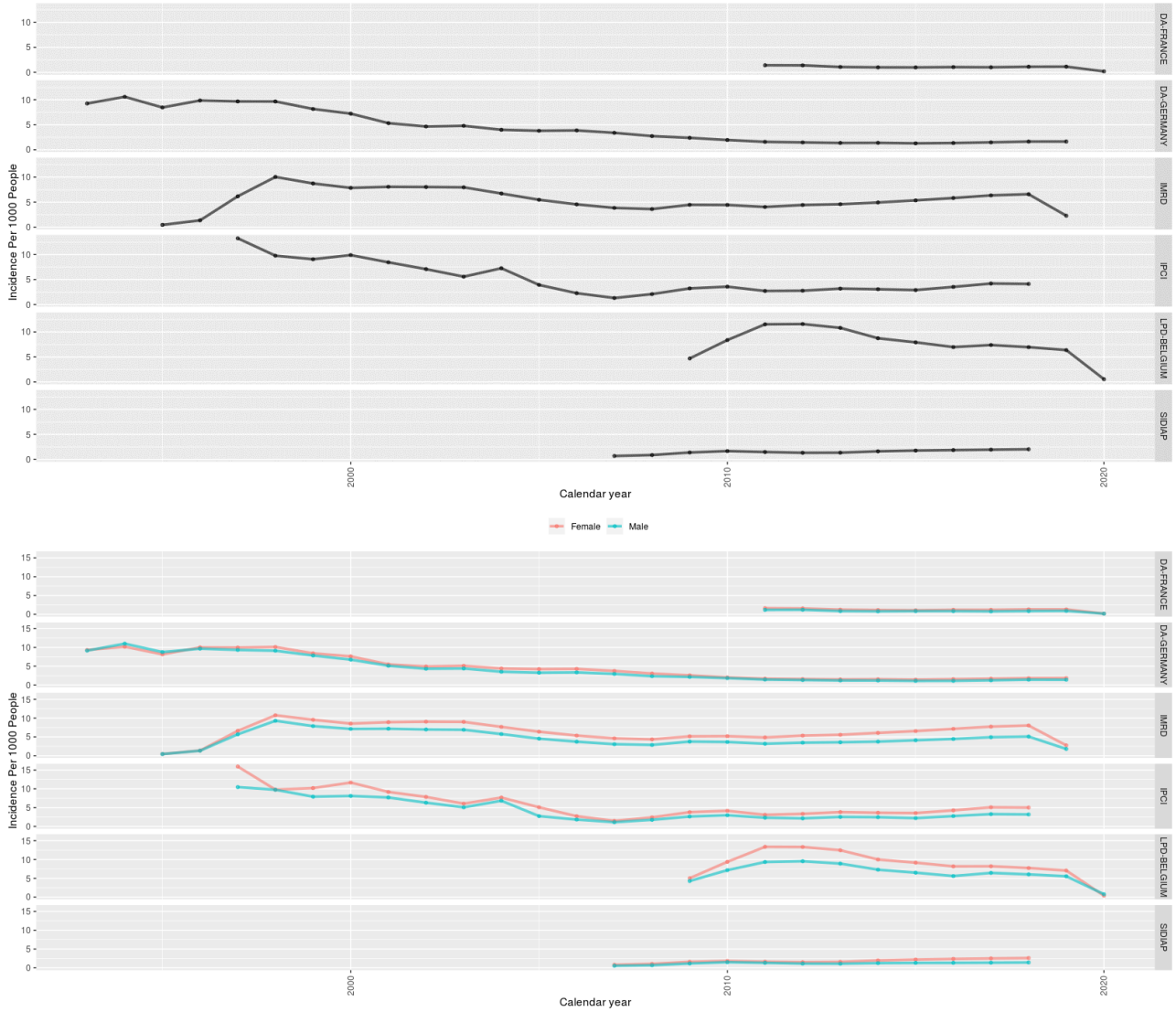

Figure 3 Incidence of H2RA over calendar year overall (top) and further stratified by gender (bottom)

Next the incidence of the individual H_2RA was explored in particular focusing on ranitidine. (Fig 4). The highest incidence of ranitidine use was reported in LPD_Belgium (11.4/1,000 persons (2012)) and the lowest new use in SIDIAP (range between 0.7/1,000 (2007) – 2.0/1,000 (2018)) and France (range between 0.9/1,000 (2015)(lowest) – 1.2/1,000 (2012)(highest)).

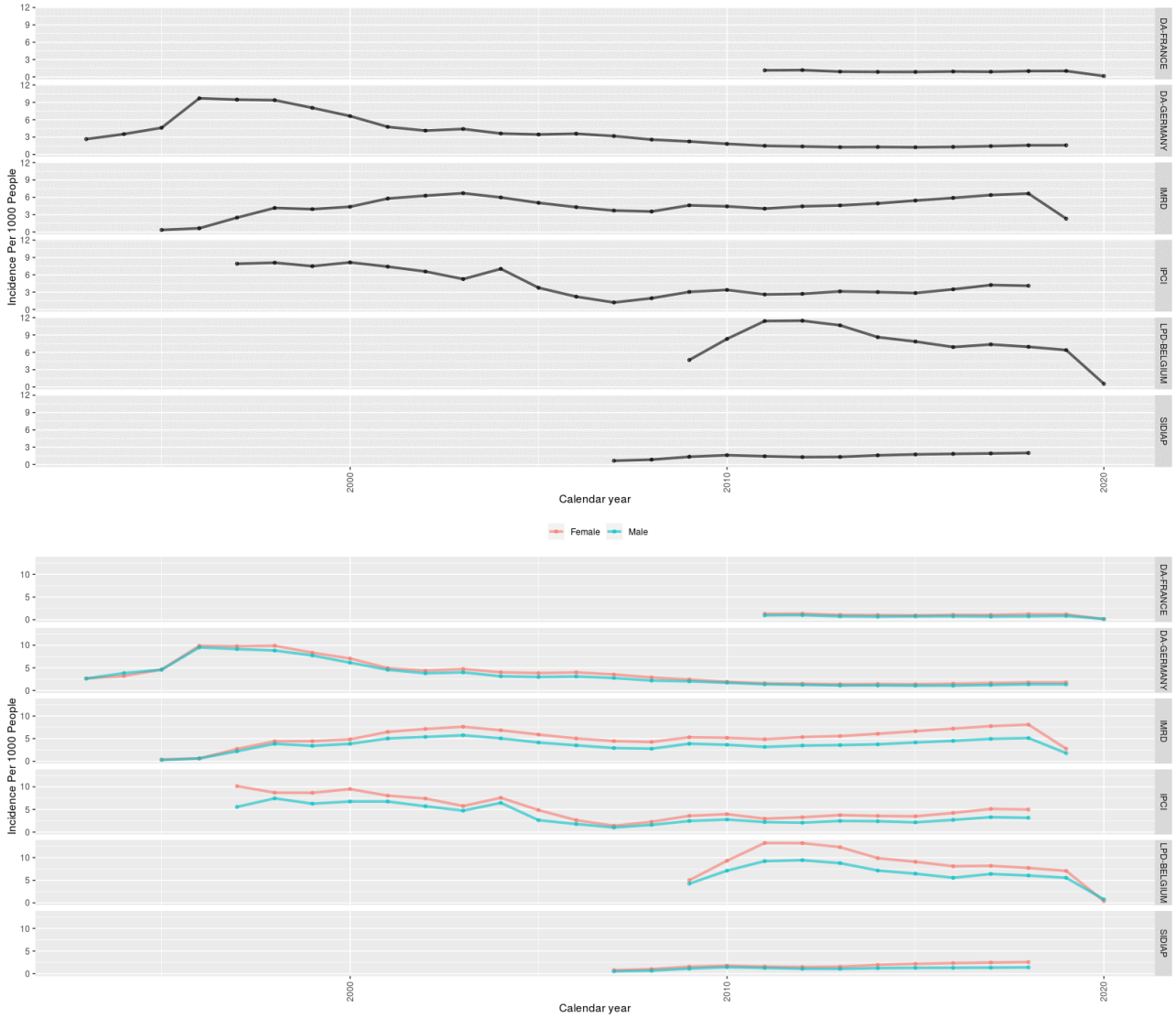

Figure 4 Incidence of ranitidine overall (top) and further stratified by gender (bottom)

As not all databases have the same duration of follow-up, we investigated the incident use pattern of ranitidine over the past complete 5 years (2014-2019) to increase comparability between databases. (Fig 5).

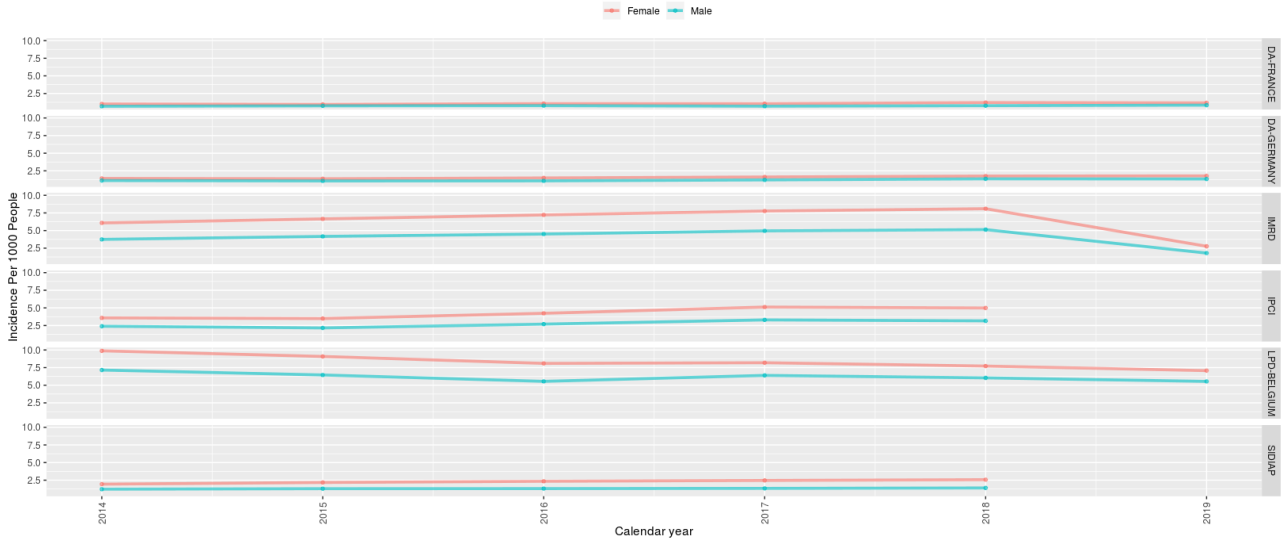

Figure 5 Incidence of ranitidine by gender and calendar year over the past 5 years

Figure 5 shows that the incidence of ranitidine use in IMRD, IPCI and LPD-Belgium are comparable, and that new use of ranitidine is much lower in DA_France, DA_Germany and SIDIAP. In all databases, new use is higher in females than in males and no further decrease in incidence rate by calendar year could be observed.

The second most used H_2RA was cimetidine especially in IPCI, the IMRD and DA_Germany which are the countries with the longest follow-up period. New use of other H_2RA (Famotidine, Nizatidine, Roxatidine, Ranitidine bismuth) was low or non-existing. (table 2 and ancillary tables)

Prevalent use of H_2RA (by class and by individual drug)

In line with the incidence, the prevalence of H_2RA over all calendar years was the highest in IMRD (34.6/1,000 persons (1994)) followed by IPCI (31.5/1,000 (1997)), LPD_Belgium (28.6/1,000 (2010)) and DA_Germany (21.8/1,000 (1992)). (Fig 6)

Prevalent H_2RA use was the lowest in DA_France (lowest and highest rates between 5.3/1,000 persons (2010) and 1.2/1,000 persons (2020)) and SIDIAP (lowest and highest rates between 1.0/1,000 persons (2007) and 3.3/1,000 persons (2018)). In DA_Germany, IPCI and LPD_Belgium use of H_2RA decreased over time. In IMRD, use decreased until 2008 from when it slightly started to increase again. (Fig 6)

When use was further explored by gender, it is clear that the prevalence of H_2RA use was higher in females than in males especially for IMRD, IPCI and LPD_Belgium. (Fig 6)

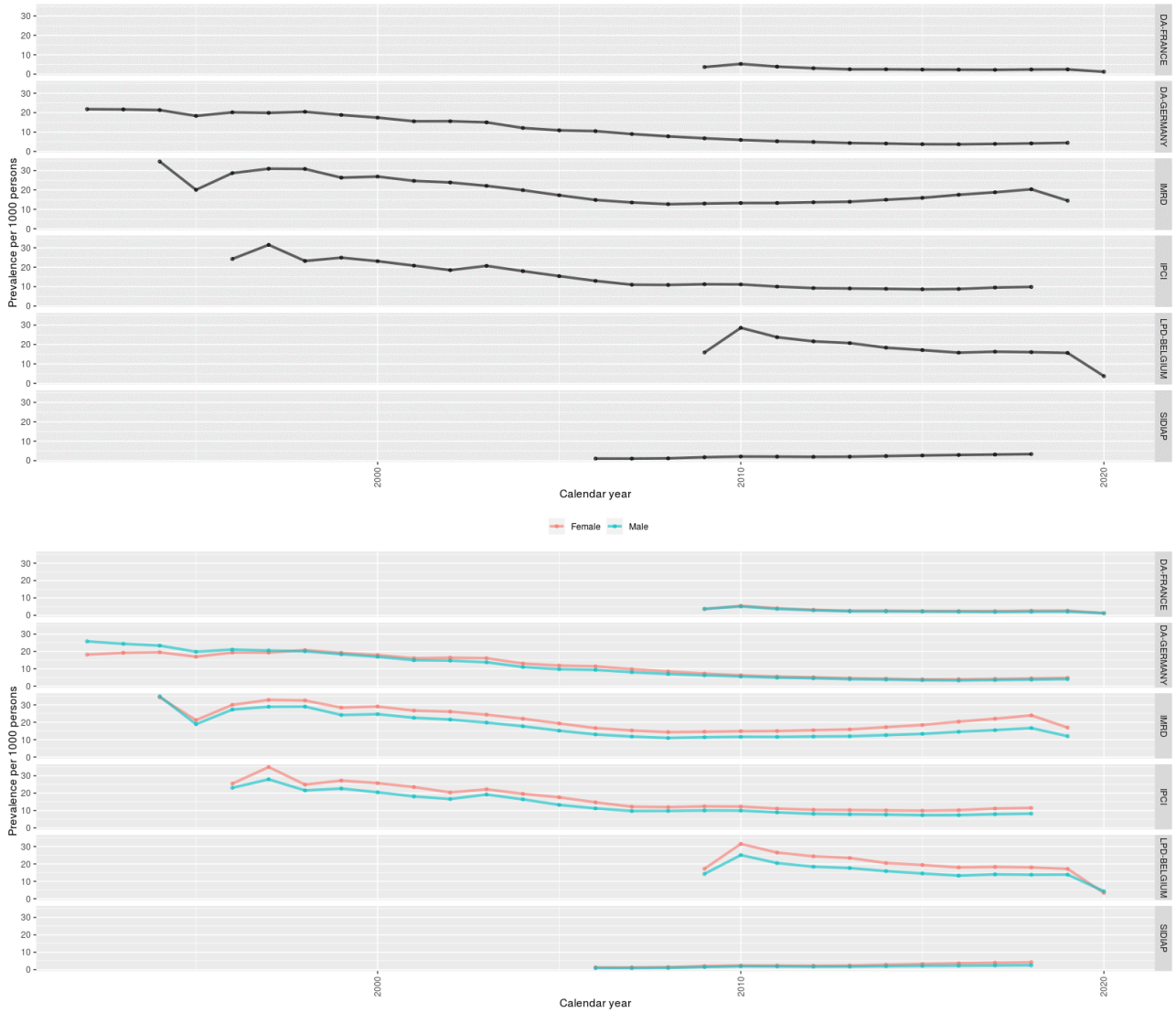

Figure 6 Prevalence of H2RA over calendar year overall (top) and further stratified by gender (bottom)

Next the prevalence of the individual H2RA – over all calendar years - was explored in particular focusing on ranitidine. (Fig 7). The highest prevalence of ranitidine use was reported in LPD_Belgium (28.3/1,000 persons (in 2010)) and the lowest prevalence in SIDIAP (lowest and highest range between 1.0/1,000 (in 2006) and 3.3/1,000 (in 2018)).

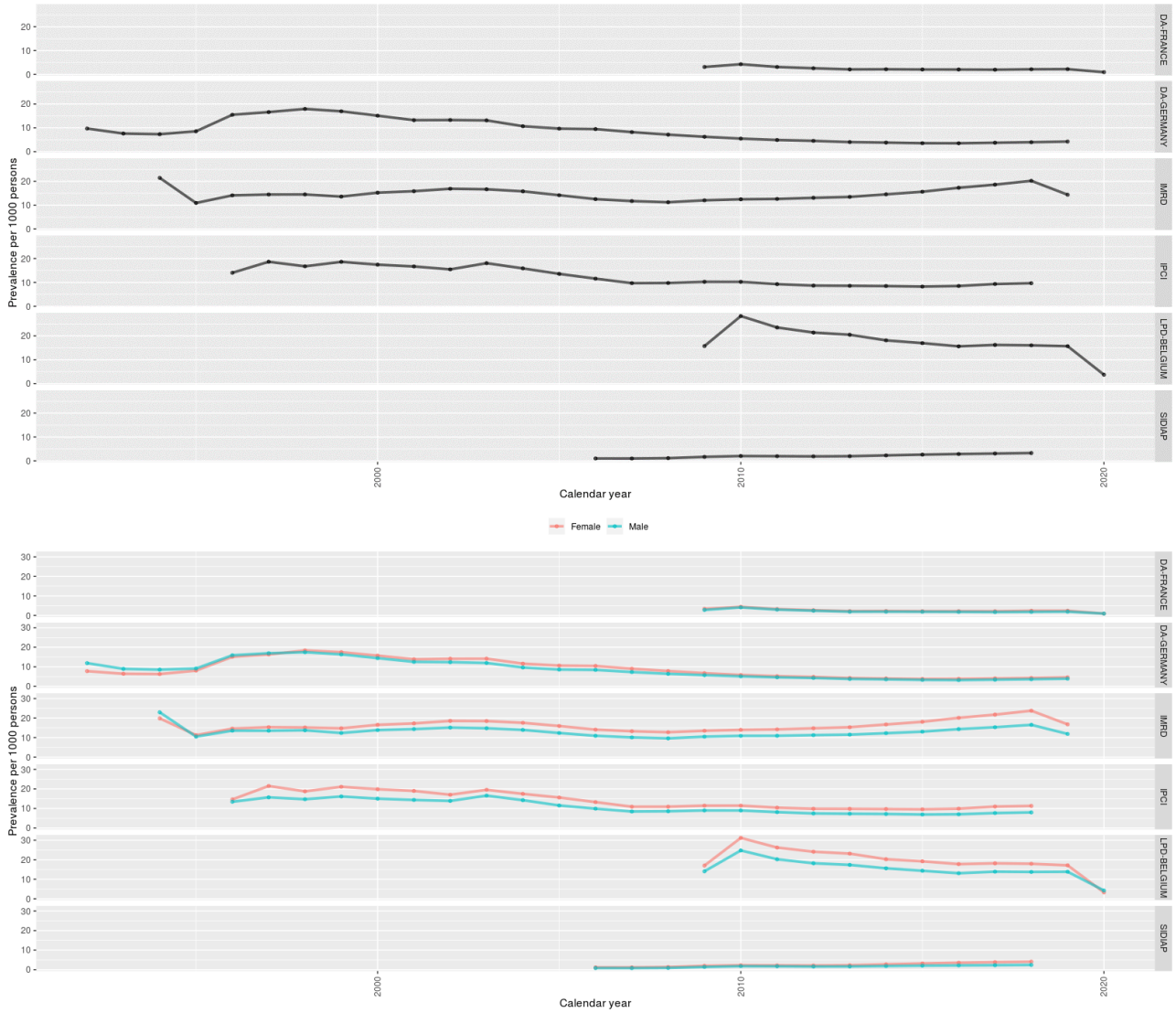

Figure 7 Prevalence of ranitidine over calendar year overall (top) and further stratified by gender (bottom)

As not all databases have the same duration of follow-up, we investigated the prevalent use pattern of ranitidine over the past complete 5 years (2014-2019) to increase comparability between databases. (Fig 8).

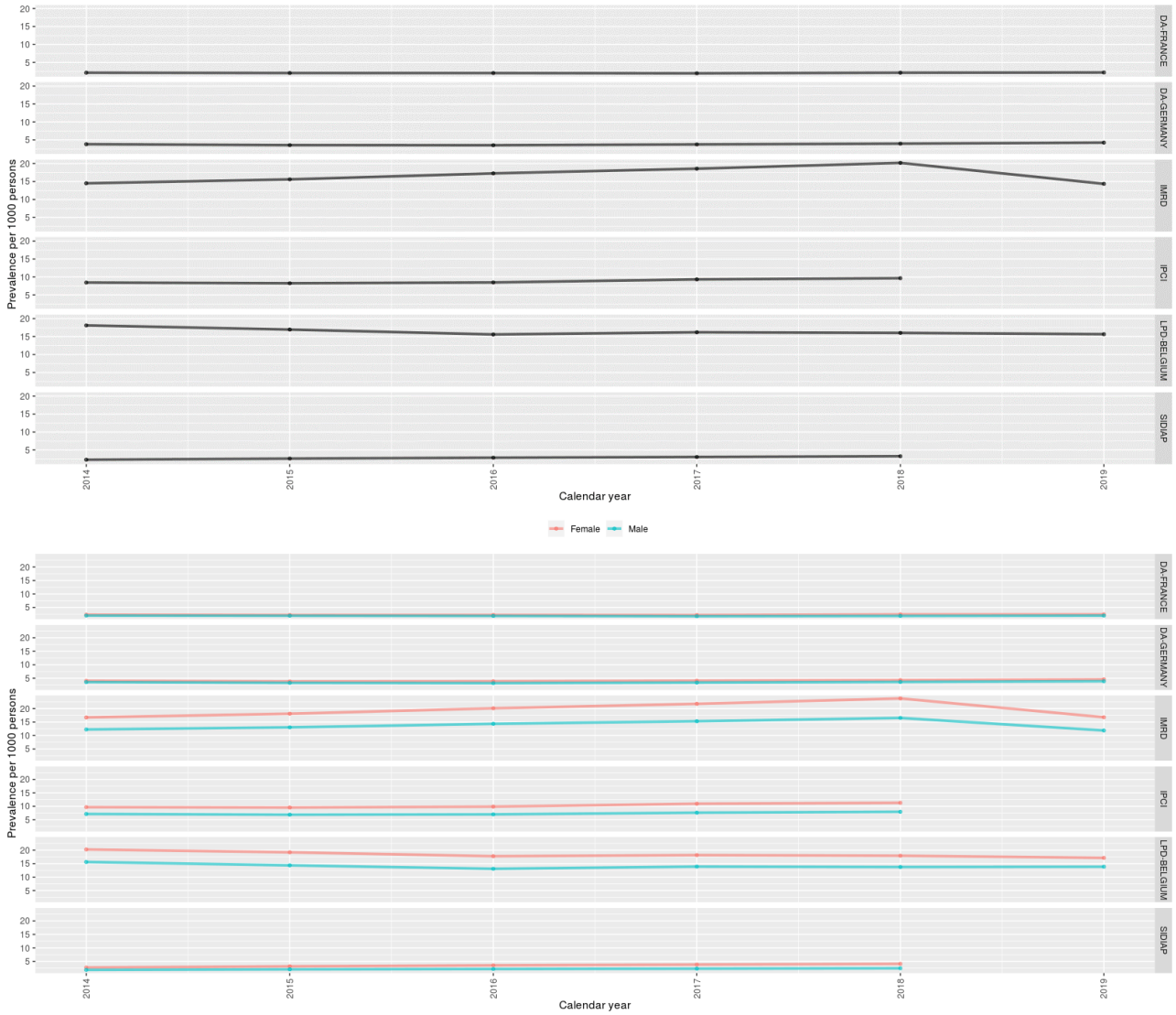

Figure 8 Prevalence of ranitidine by gender and calendar year over the past 5 years (2014-2019)

Figure 8 shows the highest prevalence of ranitidine use in LPD_Belgium and IMRD, followed by IPCI. Use of ranitidine is much lower in DA_France, DA_Germany and SIDIAP. In all databases, prevalence of ranitidine use is higher in females than in males (mainly obvious in databases with larger prevalence numbers) and no further decrease in prevalence by calendar year could be observed.

With regard to the other type of H_2RA, mainly cimetidine was used but with lower prevalences than ranitidine and use dropped almost to 0 over calendar time. The use of the other H_2RA (Famotidine, Nizatidine, Roxatidine, Ranitidine bismuth) was low or non-existing. (table 2)

Table 2 Incidence and prevalence of use of H_2 receptor antagonists by class and by individual drugs

	DA France		DA Germany		IMRD#		IPCI		LPD Belgium		SIDIAP	
Incidence												
H_2 receptor antagonist	2011-2019		1993-2019		1997-2018		1997-2018		2009-2019		2007-2018	
Incidence	1.4	1.1	9.2	1.6	6.2	6.6	13.2	4.1	4.7	6.4	0.7	2.0
Ranitidine	2011-2019		1993-2019		1997-2019		1997-2018		2009-2019		2007-2018	
Incidence	1.1	1.0	2.6	1.6	2.5	6.6	7.9	4.1	4.7	6.4	0.7	2.0
Cimetidine	2011-2019		1993-2019		1997-2019		1997-2018		2009-2018		2007-2011	
Incidence	0.2	0.2	4.9	0.04	3.1	<0.05	5.2	<0.05	<0.05	<0.05	<0.05	<0.05

Famotidine	2011-2019		1993-2019		1997-2018		1997-2018				2007-2018	
Incident	0.05	<0.05	1.6	<0.05	<0.05	<0.05	0.8	<0.05			<0.05	<0.05
Nizatidine	2012-2014		1993-2005		1998-2019							
Incident	<0.05	<0.05	1.3	<0.05	2.2	<0.05						
Roxatidine			1992-2002								2007	
Incident			1.2	<0.05							<0.05	<0.05
Raniditine Bismuth					1996-2007						2007-2008	
Incident					<0.05	<0.05					<0.05	<0.05
Prevalence												
Prevalence	DA France		DA Germany		IMRD[#]		IPCI		LPD Belgium		SIDIAP	
H_2 receptor antagonist	2009-2019		1992-2019		1994-2019		1996-2018		2009-2019		2006-2018	
Prevalence	3.7	2.5	21.8	4.4	34.6	14.5	24.3	9.8	15.9	15.7	1.1	3.3
Ranitidine	2009-2019		1992-2019		1994-2019		1996-2018		2009-2019		2006-2018	
Prevalence	3.1	2.2	9.7	4.3	21.4	14.4	14.0	9.7	15.7	15.7	1.0	3.3
Cimetidine	2009-2019		1992-2019		1994-2019		1996-2018		2009-2018		2006-2013	
Prevalence	0.5	0.3	7.0	0.1	13.8	0.1	9.3	0.1	0.2	<0.05	<0.05	<0.05
Famotidine	2010-2019		1992-2019		1995-2019		1996-2018				2006-2018	
Prevalence	0.2	<0.05	4.1	0.1	0.1	<0.05	1.0	0.1			<0.05	0.1
Nizatidine	2010-2019		1992-2006		1995-2019		1996-2018					
Prevalence	<0.05	<0.05	0.9	<0.05	2.7	<0.05	0.5	<0.05				
Roxatidine			1992-2003								2007	
Prevalence			1.2	<0.05							<0.05	<0.05
Raniditine Bismuth					1996-2007						2006-2008	
Prevalence					0.06	<0.05					<0.05	<0.05

Incidence and prevalence expressed as number of users per 1,000 persons and are provided at the start and the enddate of the respective exposure cohorts. No use of lafutidine and niperotidine during follow-up. # For IMRD, incidence of H_2RA, ranitidine and cimetidine are provided 2- years later than the prevalence because of low numbers (see also graphs). No use of lafutidine and niperotidine during follow-up. Grey coloured cells mean that there was no use in the respective countries. Roxatidine and Ranitidine bismuth only available as oral product.

The incidence and prevalence of H_2RA as class, raniditine and other H_2RA, by gender and by calendar year is also provided in the ancillary tables.

Use of H_2RA, ranitidine and other H_2RA was very low in children (<10 years) with a prevalence, considering the total study period, ranging between 0.04/1,000 persons to 5.7/1,000 persons (IMRD). The prevalence increased with age with prevalences ranging between 3.7/1,000 persons (SIDIAP) to 45.0/1,000 persons (IMRD) in persons 70-79 years. From the age of 90, the prevalence decreased in all databases.

A similar pattern was observed when studying ranitidine only namely lowest prevalence in children (<10 years) 0.04/1,000 persons (SIDIAP) to 5.6/1,000 persons (IMRD) and a prevalence increasing with age (3.4/1,000 persons (SIDIAP) – 37.0/1,000 persons (IMRD) in individuals 70-79 years).

A similar pattern for the incidence of H_2RA, ranitidine and other H_2RA was observed namely low incidence in children (for H_2RA as class 0.03-2.0/1,000 persons SIDIAP and LPD_Belgium respectively), and the incidence increasing with age (1.6 (DA_France)-10.4 (IMRD)/1,000 persons in individuals between 70-79 years). With a decrease in incidence from the age of 80 years on.

Use of H_2RA and type of formulation
As can be observed in table 3, mainly H_2RA via oral formulation was prescribed and/or dispensed. Use of parenteral H_2RA was less than 2% in all databases.

Table 3 also describes the total number of users per database and per individual ingredient. From this table, it is obvious that ranitidine represented the bulk of H_2RA use.

Table 3 Number of users and number and proportion by type of formulation

Ingredient		DA-FRANCE	DA-GERMANY	IMRD	IPCI	LPD-BELGIUM	SIDIAP	Total
H2RA Class	Total	36,826	170,600	714,828	63,594	53,206	96,663	1,135,717
	Injectable Product	179 (0.49)	1,296 (0.76)	103 (0.01)	8 (0.01)	62 (0.12)	156 (0.16)	1,804 (0.16)
	Oral Product	36,647 (99.51)	169,304 (99.24)	714,547 (99.96)	62,612 (98.46)	53,144 (99.88)	96,435 (99.76)	1,132,689 (99.73)
	Unknown			178 (0.02)	974 (1.53)		72 (0.07)	1,224 (0.11)
Ranitidine	Total	31,613	150,513	615,485	61,063	52,683	94,962	1,006,319
	Injectable Product	127 (0.4)	919 (0.61)	97 (0.02)	8 (0.01)	62 (0.12)	157 (0.17)	1,370 (0.14)
	Oral Product	31,486 (99.6)	149,594 (99.39)	615,388 (99.98)	60,170 (98.54)	52,621 (99.88)	94,740 (99.77)	1,003,999 (99.77)
	Unknown				885 (1.45)		65 (0.07)	950 (0.09)
Cimetidine	Total	4,989	13,063	99,287	2,364	642	275	120,620
	Injectable Product	56 (1.12)	443 (3.39)	8 (0.01)			0 (0)	507 (0.42)
	Oral Product	4,933 (98.88)	12,620 (96.61)	99,099 (99.81)	2,275 (96.24)	642 (100)	263 (95.64)	119,832 (99.35)
	Unknown			180 (0.18)	89 (3.76)		10 (3.64)	279 (0.23)
Nizatidine	Total	84	3,010	35,234	71		0	38,399
	Injectable Product			0 (0)				0 (0)
	Oral Product	84 (100)	3,010 (100)	35,232 (99.99)	70 (98.59)		0	38,396 (99.99)
	Unknown				0 (0)			0 (0)
Famotidine	Total	658	13,254	2,257	704		2,092	18,965
	Injectable Product		27 (0.2)					27 (0.14)
	Oral Product	658 (100)	13,227 (99.8)	2,232 (98.89)	696 (98.86)		2,092 (100)	18,905 (99.68)
	Unknown			25 (1.11)	8 (1.14)			33 (0.17)
Roxatidine	Total		1,122		0		8	1,130
	Oral Product		1,122 (100)				8 (100)	1,130 (100)
Ranitidine bismuth	Total			460	0		36	496
	Oral Product			460 (100)			36 (100)	496 (100)

10.3. Cumulative drug exposure of H_2RA, ranitidine and other H_2RA

The median cumulative duration of H_2RA ranged between 28 days (P5-P95=7-488) in DA_France to 60 days in IMRD (P5-P95=15-1,860). (table 4) In all databases, the median cumulative duration of H_2RA was highest in patients >75 years. In all databases, except for DA_France and IPCI, the median duration was lower for parenteral use (range 2 (DA_Germany) to 10 days (LPD_Belgium and SIDIAP) compared to oral use but number of patients with parenteral use was low. No differences in median duration within different indications of use was observed except for IMRD where cumulative duration was the lowest in patients with reflux disease. (see ancillary tables)

Next, the cumulative drug exposure was explored for the individual H_2RA starting with ranitidine. As ranitidine represents the bulk of H_2RA use, results for ranitidine are similar to the H_2RA results.

(table 4) The median cumulative duration of ranitidine ranged between 28 days (P5-P95=7-480) in DA_France to 60 days in IMRD (P5-P95=15-1,800). In all databases, the median cumulative duration of ranitidine was highest in patients >75 years (median cumulative duration of 60 days (DA_France) – 502 days (SIDIAP). In all databases, except for DA_France and IPCI, the median duration was lower for parenteral use.

The median duration of cimetidine ranged between 25 days (P5-P95=5-650) in DA_Germany to 75 days in IPCI (P5-P95=10-1,800). Also, for cimetidine, in all databases, the median cumulative duration was highest in patients >75 years. No differences in median duration of use between indications was observed.

The median duration of famotidine use was high in IMRD (120 days; P5-P95=14-2,962) and IPCI (289 days; P5-P95=15-2,428) whereas it ranged between 30 (DA_France), 40 (DA_germany) and 60 days (SIDIAP) in the other databases. The median duration of the other H_2RA as well as the number of patients by ICH exposure category is described in table 4&5 as well as in the ancillary documents.

Next cumulative exposure was categorised according to the ICH guidelines on the assessment and control of DNA reactive impurities in pharmaceuticals. (EMA 2015) (table 4&5)

The proportion of patients using ranitidine for a duration between 1-10 years was low and ranged between 6.5-18.8% (DA_France and IMRD respectively). Use of ranitidine for more than 10 years was neglectable and ranged between 0.03-3.3% (DA_Germany and SIDIAP respectively). The proportion of patients using cimetidine for a duration between 1-10 years was low and ranged between 5.3-23.7% (LPD Belgium and IPCI respectively). Use of cimetidine for more than 10 years was neglectable and ranged between 0.04-0.8% (DA_France and IMRD respectively) (table 5).

As use of other H_2RA (Famotidine, Nizatidine, Roxatidine, Ranitidine bismuth) was low or non-existing, the cumulative duration is not described in detail but is available in table 4, 5 and in the ancillary tables.

Table 4 Cumulative duration in days for H_2RA, ranitidine and other individual H_2RA

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
H2 Class																		
Total	36,826	28	7 - 488	170,600	40	10 - 1,300	714,828	60	15 - 1,860	63,594	40	10 - 1,448	53,206	56	14 - 712	96,663	58	4 - 2,716
Age 0-18	1,858	15	5 - 84	6,804	20	5 - 100	69,777	30	15 - 330	8,445	40	9 - 350	5,064	42	14 - 360	2,484	24	4 - 182
Age 18-75	30,537	28	7 - 422	144,885	40	10 - 1,250	530,639	60	15 - 1,950	48,163	30	10 - 1,530	43,038	56	14 - 712	82,714	58	4 - 2,218
Age 75+	4,431	60	10 - 896	18,911	100	10 - 1,700	114,412	142	21 - 2,078	6,986	135	14 - 1,905	5,104	84	15 - 1,232	11,465	494	5 - 4,647
Inject	179	30	7 - 150	1,296	2	1 - 9	103	30	30 - 177	8	30	1 - 90	62	10	2 - 117	156	10	2 - 530
Oral	36,647	28	7 - 490	169,304	41	10 - 1,300	714,547	60	15 - 1,860	62,612	38	10 - 1,470	53,144	56	14 - 714	96,435	58	4 - 2,718
Unknown							178	89	20 - 678	974	60	15 - 430				72	24	2 - 364
Dur < 1 m	20,102	15	5 - 28	75,233	20	5 - 24	95,828	15	3 - 28	22,751	15	6 - 20	22,128	28	14 - 28	32,682	12	2 - 29
Dur 1-12 m	14,302	84	30 - 280	71,881	80	34 - 300	474,420	60	30 - 270	29,590	60	30 - 300	26,276	70	30 - 280	43,019	58	30 - 273
Dur 1-10 y	2,412	680	392 - 2,107	21,977	870	400 - 2,865	135,445	944	408 - 2,912	11,122	920	405 - 2,700	4,704	784	392 - 2,643	17,816	1012	404 - 3,093
Dur > 10 y	10	4326	3,735 - 6,603	1,509	4600	3,700 - 8,868	9,135	4528	3,720 - 7,122	131	3990	3,675 - 5,670	98	4466	3,752 - 6,387	3,146	5139	3,740 - 8,214
Ranitidine																		
Total	31,613	28	7 - 480	150,513	40	10 - 1,300	615,485	60	15 - 1,800	61,063	34	10 - 1,418	52,683	56	14 - 716	94,962	58	4 - 2,714
Age 0-18	1,643	15	5 - 84	6,264	20	5 - 100	67,286	30	24 - 330	8,293	40	10 - 350	4,910	42	14 - 360	2,439	24	4 - 182
Age 18-75	26,204	28	7 - 420	126,350	40	10 - 1,250	447,728	60	15 - 1,918	46,159	30	10 - 1,440	42,712	56	14 - 712	81,426	58	4 - 2,202
Age 75+	3,766	60	10 - 899	17,899	100	10 - 1,700	100,471	140	28 - 2,040	6,611	120	14 - 1,860	5,061	84	15 - 1,232	11,097	502	6 - 4,729
Inject	127	30	6 - 150	919	1	1 - 8	97	30	30 - 126	8	30	1 - 90	62	10	2 - 117	157	9	2 - 521
Oral	31,486	28	7 - 480	149,594	40	10 - 1,300	615,388	60	15 - 1,800	60,170	30	10 - 1,440	52,621	56	14 - 716	94,740	58	4 - 2,718
Unknown										885	60	17 - 400				65	19	1 - 136
Dur < 1 m	17,556	15	5 - 28	67,175	20	5 - 21	72,910	15	4 - 28	22,326	15	6 - 20	21,963	28	14 - 28	32,053	12	2 - 29
Dur 1-12 m	11,995	84	30 - 280	62,582	80	34 - 300	419,499	58	30 - 270	28,343	60	30 - 300	25,948	70	30 - 280	42,538	58	30 - 272
Dur 1-10 y	2,054	681	392 - 2,100	19,456	860	400 - 2,850	115,794	930	408 - 2,892	10,281	901	405 - 2,690	4,675	784	392 - 2,640	17,261	1014	406 - 3,090
Dur > 10 y	8	4326	3,716 - 6,313	1,300	4600	3,700 - 8,887	7,282	4502	3,720 - 7,010	113	4008	3,678 - 5,670	97	4448	3,752 - 6,388	3,110	5147	3,738 - 8,227
Cimetidine																		
Total	4,989	28	5 - 420	13,063	25	5 - 650	99,287	33	14 - 1,512	2,364	75	10 - 1,800	642	56	6 - 420	275	31	2 - 1,675
Age 0-18	211	20	5 - 72	273	20	4 - 100	2,528	30	10 - 144	156	30	8 - 180	164	56	10 - 120	23	28	2 - 84
Age 18-75	4,155	28	5 - 365	12,299	25	6 - 640	82,353	30	14 - 1,432	1,867	74	11 - 1,836	417	40	6 - 617	205	31	2 - 1,593
Age 75+	623	56	8 - 671	491	50	3 - 1,305	14,406	90	14 - 1,855	341	180	15 - 1,950	61	56	20 - 450	47	61	2 - 1,753
Inject	56	30	10 - 176	443	3	3 - 9	8	30	30 - 435									-
Oral	4,933	28	5 - 420	12,620	30	7 - 700	99,099	32	14 - 1,512	2,275	80	14 - 1,810	642	56	6 - 420	263	31	2 - 1,704
Unknown							180	90	25 - 782	89	60	7 - 756				10	20	2 - 467
Dur < 1 m	2,576	15	5 - 28	6,705	20	3 - 25	23,434	15	1 - 28	618	15	7 - 20	228	20	6 - 28	131	2	2 - 26
Dur 1-12 m	2,133	60	30 - 270	5,338	60	31 - 280	59,765	56	30 - 270	1,182	90	30 - 315	379	60	30 - 240	101	60	31 - 272
Dur 1-10 y	278	645	383 - 2,073	960	800	400 - 2,800	15,296	927	404 - 2,884	559	915	420 - 2,790	34	735	420 - 2,279	43	1123	369 - 2,583

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
Dur > 10 y			-	60	4902	3,733 - 9,555	792	4380	3,722 - 7,240	5	4110	3,834 - 4,857			-			
Nizatidine																		
Total	84	30	10 - 1,060	3,010	20	10 - 443	35,234	56	14 - 1,662	71	180	12 - 2,070	No use			No use		-
Age 0-18			-	59	20	10 - 122	269	28	14 - 112									
Age 18-75	69	30	10 - 960	2,877	20	10 - 450	27,680	30	14 - 1,620	58	145	10 - 2,160						-
Age 75+	14	44	28 - 680	74	50	20 - 410	7,285	112	14 - 1,830	13	630	91 - 1,656						
Inject									-									
Oral	84	30	10 - 1,060	3,010	20	10 - 443	35,232	56	14 - 1,662	70	180	12 - 2,079						-
Unknown												-						
Dur < 1 m	36	15	10 - 28	1,624	20	10 - 20	11,568	28	7 - 28	10	15	6 - 19						-
Dur 1-12 m	36	65	30 - 308	1,206	50	40 - 242	17,085	60	30 - 300	33	90	30 - 282						-
Dur 1-10 y	12	696	466 - 1,378	176	797	400 - 2,340	6,234	930	410 - 2,856	28	900	520 - 2,511						
Dur > 10 y						-	347	4620	3,696 - 6,946									
Famotidine																		
Total	658	30	14 - 648	13,254	40	10 - 1,020	2,257	120	14 - 2,962	704	289	15 - 2,428	No use			2,092	61	2 - 2,683
Age 0-18	11	28	7 - 64	287	20	10 - 241	9	48	3 - 734			-				26	18	2 - 495
Age 18-75	529	29	14 - 570	11,812	30	10 - 900	1,822	112	14 - 3,108	556	270	15 - 2,430				1,572	56	2 - 2,536
Age 75+	118	84	15 - 766	1,155	100	10 - 1,715	426	252	14 - 2,506	145	382	15 - 2,346				494	366	4 - 2,984
Inject				27	3	3 - 16												
Oral	658	30	14 - 648	13,227	40	10 - 1,020	2,232	120	14 - 2,968	696	300	15 - 2,430				2,092	61	2 - 2,683
Unknown							25	60	13 - 1,010	8	75	17 - 1,594						
Dur < 1 m	300	15	7 - 28	6,255	20	10 - 20	658	28	6 - 28	77	15	5 - 23				801	13	2 - 29
Dur 1-12 m	301	84	30 - 280	5,490	70	40 - 300	823	112	42 - 336	315	90	30 - 360				603	86	31 - 314
Dur 1-10 y	57	756	414 - 1,691	1,421	850	400 - 2,850	701	1064	446 - 2,970	305	1080	450 - 2,728				647	914	366 - 3,109
Dur > 10 y				88	4210	3,700 - 6,198	75	4879	3,752 - 8,205	7	3890	3,708 - 6,190				41	4536	3,683 - 7,522
Roxatidine																		
Total	No use			1,122	20	10 - 469	No use			No use			No use			8	52	2 - 1,293
Age 0-18				34	35	6 - 1,574												
Age 18-75				1,081	20	10 - 424										5	306	2 - 1,514
Age 75+				7	30	20 - 440												-
Oral				1,122	20	10 - 469										8	52	2 - 1,293
Dur < 1 m				634	12	10 - 24												-
Dur 1-12 m				417	50	30 - 250												-
Dur 1-10 y				71	746	372 - 2,500												-
Ranitidine bismuth citrate	No use			No use						No use			No use					

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
Total							460	14	7 - 56			-				36	2	2 - 19
Age 0-18									-							5	4	2 - 15
Age 18-75							424	14	7 - 56			-				29	2	2 - 24
Age 75+							34	7	5 - 66									-
Oral							460	14	7 - 56			-				36	2	2 - 19
Dur < 1 m							426	7	7 - 28			-				35	2	2 - 15
Dur 1-12 m							31	56	32 - 210			-						
Dur 1-10 y									-									-

Inject = Injectable thus parenteral administration, med = median

Table 5 Number of users and proportion by ICH exposure category

	DA-FRANCE	DA-GERMANY	IMRD	IPCI	LPD-BELGIUM	SIDIAP	Total
H_2 Class	36,826	170,600	714,828	63,594	53,206	96,663	1,135,717
<= 1 month	20,102 (54.59)	75,233 (44.10)	95,828 (13.41)	22,751 (35.78)	22,128 (41.59)	32,682 (33.81)	268,724 (23.66)
>1-12 months	14,302 (38.84)	71,881 (42.13)	474,420 (66.37)	29,590 (46.53)	26,276 (49.39)	43,019 (44.50)	659,488 (58.07)
>1-= 10 years	2,412 (6.55)	21,977 (12.88)	135,445 (18.95)	11,122 (17.49)	4,704 (8.84)	17,816 (18.43)	193,476 (17.04)
>10 years	10 (0.03)	1,509 (0.88)	9,135 (1.28)	131 (0.21)	98 (0.18)	3,146 (3.25)	14,029 (1.24)
Ranitidine	31,613	150,513	615,485	61,063	52,683	94,962	1,006,319
<= 1 month	17,556 (55.53)	67,175 (44.63)	72,910 (11.85)	22,326 (36.56)	21,963 (41.69)	32,053 (33.75)	233,983 (23.25)
>1-12 months	11,995 (37.94)	62,582 (41.58)	419,499 (68.16)	28,343 (46.42)	25,948 (49.25)	42,538 (44.79)	590,905 (58.72)
>1-= 10 years	2,054 (6.50)	19,456 (12.93)	115,794 (18.81)	10,281 (16.84)	4,675 (8.87)	17,261 (18.18)	169,521 (16.85)
>10 years	8 (0.03)	1,300 (0.86)	7,282 (1.18)	113 (0.19)	97 (0.18)	3,110 (3.27)	11,910 (1.18)
Cimetidine	4,989	13,063	99,287	2,364	642	275	120,620
<= 1 month	2,576 (51.63)	6,705 (51.33)	23,434 (23.60)	618 (26.14)	228 (35.51)	131 (47.64)	33,692 (27.93)
>1-12 months	2,133 (42.75)	5,338 (40.86)	59,765 (60.19)	1,182 (50.00)	379 (59.03)	101 (36.73)	68,898 (57.12)
>1-= 10 years	278 (5.57)	960 (7.35)	15,296 (15.41)	559 (23.65)	34 (5.30)	43 (15.64)	17,170 (14.23)
>10 years	2 (0.04)	60 (0.46)	792 (0.80)	5 (0.21)	1 (0.16)	0 (0.00)	860 (0.71)
Nizatidine	84	3,010	35,234	71	No use	No use	38,399
<= 1 month	36 (42.86)	1,624 (53.95)	11,568 (32.83)	10 (14.08)			13,238 (34.47)
>1-12 months	36 (42.86)	1,206 (40.07)	17,085 (48.49)	33 (46.48)			18,360 (47.81)
>1-= 10 years	12 (14.29)	176 (5.85)	6,234 (17.69)	28 (39.44)			6,450 (16.80)
>10 years	0 (0.00)	< 5	347 (0.98)	0 (0.00)			351 (0.91)
Famotidine	658	13,254	2,257	704	No use	2,092	18,965
<= 1 month	300 (45.59)	6,255 (47.19)	658 (29.15)	77 (10.94)		801 (38.29)	8,091 (42.66)

	DA-FRANCE	DA-GERMANY	IMRD	IPCI	LPD-BELGIUM	SIDIAP	Total
>1-12 months	301 (45.74)	5,490 (41.42)	823 (36.46)	315 (44.74)		603 (28.82)	7,532 (39.72)
>1-= 10 years	57 (8.66)	1,421 (10.72)	701 (31.06)	305 (43.32)		647 (30.93)	3,131 (16.51)
>10 years	0 (0.00)	88 (0.66)	75 (3.32)	7 (0.99)		41 (1.96)	211 (1.11)
Roxatidine	No use	1,122	No use	No use	No use	8	1,130
<= 1 month		634 (56.51)				< 5	638 (56.46)
>1-12 months		417 (37.17)				< 5	420 (37.17)
>1-= 10 years		71 (6.33)				< 5	72 (6.37)
>10 years		0 (0.00)				0 (0.00)	0 (0.00)
Ranitidine bismuth	No use	No use	460	No use	No use	36	496
<= 1 month			426 (92.61)			35 (97.22)	461 (92.94)
>1-12 months			31 (6.74)			0 (0.00)	31 (6.25)
>1-= 10 years			< 5			< 5	< 5
>10 years			0 (0.00)			0 (0.00)	0 (0.00)

10.4. PDD/DDD ratio for H_2RA as class, ranitidine and other H_2RA

In table 6, we describe the PDD/DDD ratio of the first prescription for H_2RA as class and for ranitidine and cimetidine. The PDD/DDD ratio is the prescribed daily dose divided by the defined daily dose.

In all databases, both for the H_2RA as class, for ranitidine and the other individual H_2RA, the median PDD/DDD ratio was around 1 implying that the patient was prescribed the drug in agreement with the dose recommendations from the WHO. The median PDD/DDD ratio for cimetidine was 0.5 in DA_France and 0.25 in SIDIAP, whereas it was 1 for the other H_2RA in the French database. From the Summary of Product Characteristics of cimetidine, we know that the maintenance dose is 400 mg instead of 800 mg which might explain this finding.

In all databases, except for DA_Germany and SIDIAP, the median PDD/DDD ratio was lower in children which seems plausible as no child specific DDD recommendation is available and thus for the calculation of the PDD/DDD ratio, the suggested dose per day for the H_2RA indication for its main indication in adults is used.

The median PDD/DDD ratio was comparable for the different indications for H_2RA use. With regard to formulation, mainly lower median PDD/DDD ratio were reported (range between 0.1-0.3) for parenteral use in all databases (except for DA_Germany).

As the use of other individual H_2RA is low (famotidine, nizatidine, roxatidine, ranitidine bismuth), the median PDD/DDD ratio of these drugs is not described in table 6 but is available in the ancillary documents.

Table 6 PDD/DDD ratio for H_2RA class, ranitidine and cimetidine

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
H2 Class																		
Total	29,320	1.00	0.25 - 1.50	169,785	1.00	0.50 - 1.00	714,482	1.00	0.25 - 1.00	62,380	1.00	0.17 - 1.50	32,129	1.00	0.50 - 1.00	91,170	1.00	0.50 - 1.00
Age 0-18	1,430	0.50	0.25 - 1.00	6,740	1.00	0.50 - 1.00	69,756	0.50	0.17 - 1.00	7,553	0.30	0.05 - 1.00	3,340	0.50	0.08 - 1.00	2,382	1.00	0.50 - 1.00
Age 18-75	24,363	1.00	0.25 - 1.50	144,252	1.00	0.50 - 1.00	530,424	1.00	0.50 - 1.00	47,886	1.00	0.50 - 1.50	25,770	1.00	0.50 - 1.00	77,916	1.00	0.50 - 1.00
Age 75+	3,527	1.00	0.25 - 1.00	18,793	1.00	0.50 - 1.00	114,302	1.00	0.50 - 1.00	6,941	1.00	0.50 - 2.00	3,019	1.00	0.50 - 1.00	10,872	1.00	0.50 - 1.00
Inject	34	0.33	0.17 - 0.33	483	0.83	0.42 - 0.96	100	0.09	0.01 - 0.47	5	0.08	0.04 - 0.16	59	0.08	0.05 - 0.42	118	0.04	0.03 - 0.28
Oral	29,286	1.00	0.25 - 1.50	169,302	1.00	0.50 - 1.00	714,256	1.00	0.25 - 1.00	62,375	1.00	0.17 - 1.50	32,070	1.00	0.50 - 1.00	90,998	1.00	0.50 - 1.00
Unknown							126	0.42	0.00 - 1.00			-				54	0.17	0.17 - 1.12
Dur < 1 m	16,604	1.00	0.25 - 1.50	74,422	1.00	0.50 - 1.00	95,813	1.00	0.50 - 1.00	22,562	1.00	0.50 - 1.00	12,766	1.00	0.50 - 2.00	29,082	1.00	0.50 - 1.00
Dur 1-12 m	10,637	1.00	0.25 - 1.00	71,877	1.00	0.50 - 1.00	474,236	1.00	0.17 - 1.00	28,654	1.00	0.10 - 1.00	16,673	1.00	0.30 - 1.00	42,167	1.00	0.50 - 1.00
Dur 1-10 y	2,074	1.00	0.25 - 1.50	21,977	1.00	0.50 - 1.00	135,318	1.00	0.50 - 1.00	11,033	1.00	0.50 - 2.00	2,649	1.00	0.50 - 1.00	16,973	1.00	0.50 - 1.00
Dur > 10 y	5	0.50	0.30 - 1.00	1,509	1.00	0.50 - 1.00	9,115	1.00	0.50 - 1.00	131	1.00	0.34 - 1.50	41	1.00	0.50 - 1.00	2,948	1.00	0.50 - 1.00
Ranitidine																		
Total	25,464	1.00	0.50 - 1.50	149,667	1.00	0.50 - 1.00	615,265	1.00	0.17 - 1.00	59,940	1.00	0.17 - 1.07	32,175	1.00	0.50 - 1.00	89,692	1.00	0.50 - 1.00
Age 0-18	1,277	0.50	0.25 - 1.00	6,199	1.00	0.50 - 1.00	67,266	0.33	0.17 - 1.00	7,410	0.29	0.05 - 1.00	3,344	0.50	0.08 - 1.00	2,346	1.00	0.50 - 1.00
Age 18-75	21,130	1.00	0.50 - 1.50	125,690	1.00	0.50 - 1.00	447,608	1.00	0.50 - 1.00	45,951	1.00	0.50 - 1.50	25,802	1.00	0.50 - 1.00	76,798	1.00	0.50 - 1.00
Age 75+	3,057	1.00	0.50 - 1.50	17,778	1.00	0.50 - 1.00	100,391	1.00	0.50 - 1.00	6,579	1.00	0.50 - 1.88	3,029	1.00	0.50 - 1.00	10,548	1.00	0.50 - 1.00
Inject	34	0.33	0.17 - 0.33	73	0.83	0.18 - 0.83	94	0.08	0.01 - 0.33	5	0.08	0.04 - 0.16	59	0.08	0.05 - 0.42	119	0.03	0.03 - 0.27
Oral	25,430	1.00	0.50 - 1.50	149,594	1.00	0.50 - 1.00	615,171	1.00	0.17 - 1.00	59,935	1.00	0.17 - 1.07	32,116	1.00	0.50 - 1.00	89,522	1.00	0.50 - 1.00
Unknown												-				51	0.17	0.17 - 1.25
Dur < 1 m	14,597	1.00	0.25 - 1.50	66,333	1.00	0.50 - 1.00	72,909	1.00	0.50 - 1.00	22,154	1.00	0.50 - 1.00	12,777	1.00	0.50 - 2.00	28,603	1.00	0.50 - 1.00
Dur 1-12 m	9,073	1.00	0.50 - 1.00	62,578	1.00	0.50 - 1.00	419,358	1.00	0.17 - 1.00	27,466	1.00	0.10 - 1.00	16,700	1.00	0.30 - 1.00	41,714	1.00	0.50 - 1.00
Dur 1-10 y	1,790	1.00	0.50 - 1.50	19,456	1.00	0.50 - 1.00	115,727	1.00	0.50 - 1.00	10,207	1.00	0.50 - 2.00	2,657	1.00	0.50 - 1.00	16,456	1.00	0.50 - 1.00
Dur > 10 y			-	1,300	1.00	0.50 - 1.00	7,271	1.00	0.50 - 1.00	113	1.00	0.45 - 1.50	41	1.00	0.50 - 1.00	2,919	1.00	0.50 - 1.00
Cimetidine																		
Total	3,605	0.50	0.25 - 1.00	13,062	0.94	0.25 - 1.47	99,166	1.00	0.50 - 1.00	2,268	1.00	0.50 - 2.00	NA			196	0.25	0.25 - 1.00
Age 0-18	148	0.50	0.25 - 0.75	273	0.71	0.25 - 1.45	2,527	1.00	0.17 - 1.00	144	1.00	0.50 - 3.00				17	0.50	0.23 - 1.20
Age 18-75	3,033	0.50	0.25 - 1.00	12,298	0.96	0.25 - 1.47	82,261	1.00	0.50 - 1.00	1,798	1.00	0.50 - 2.00				148	0.25	0.25 - 1.00
Age 75+	424	0.50	0.25 - 1.00	491	0.71	0.25 - 1.00	14,378	1.00	0.50 - 1.00	326	1.00	0.25 - 1.78				31	0.25	0.25 - 1.00
Inject			-	443	0.83	0.83 - 0.96	8	0.29	0.02 - 0.59									-
Oral	3,605	0.50	0.25 - 1.00	12,619	0.96	0.25 - 1.47	99,033	1.00	0.50 - 1.00	2,268	1.00	0.50 - 2.00				188	0.25	0.25 - 1.00
Unknown							125	0.50	0.00 - 1.00			-				6	0.25	0.25 - 0.25
Dur < 1 m	1,996	0.50	0.25 - 1.00	6,704	1.00	0.50 - 2.00	23,420	1.00	0.50 - 1.00	600	1.00	0.50 - 2.00				73	0.38	0.25 - 1.00
Dur 1-12 m	1,393	0.50	0.25 - 1.00	5,338	0.50	0.25 - 1.00	59,714	1.00	0.50 - 1.00	1,119	1.00	0.50 - 2.00				89	0.25	0.25 - 1.00

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
Dur 1-10 y	215	0.50	0.25 - 1.00	960	0.50	0.25 - 1.43	15,245	1.00	0.50 - 1.00	544	1.00	0.25 - 1.50				34	0.25	0.25 - 1.00
Dur > 10 y			-	60	0.50	0.25 - 1.00	787	1.00	0.50 - 1.00	5	1.00	0.55 - 1.40						

Total numbers represent the number of users for whom information on PDD/DDD ratio is available, Inject= Injectable thus for parenteral administration, med = median, Dur=cumulative duration. NA= Information on PDD/DDD ratio not available for Cimetidine for LPD Belgium

10.5. Cumulative DDD for ranitidine and other H_2RA

Table 7 describes the cumulative DDD for H_2RA, ranitidine and cimetidine. The median cumulative DDD of H_2RA is the lowest (28 DDD; P5-P95= 4-392) in DA_Germany and the highest in IMRD (56 DDD; P5-P95=10-1,710). Similar results are observed when investigating ranitidine only with median cumulative DDD ranging between 28-56 DDD. The median cumulative DDD for cimetidine was lower (15 DDD (DA_France & SIDIAP) to 30 DDD (IMRD)). In IPCI the median cumulative DDD of cimetidine was 60. The differences in median cumulative DDD between countries might be explained by differences in package size.

Next the cumulative DDD was explored by gender, age category, type of formulation and indication of use. No differences with gender was observed but, in all databases, the median cumulative DDD was the lowest in the youngest age categories and highest in patients older than 75 years (table 7 and ancillary documents). The median cumulative DDD was also lower for parenteral use compared to oral use.

The median cumulative DDD was comparable irrespective of the indication of use except for IMRD where the median cumulative DDD was higher for gastroduodenal/peptic ulcer (median cumulative DDD for H_2RA and rantidine of 120 for a disease code of ulcer in the one year prior to treatment vs. 35 for GERD in the one year prior) (see ancillary documents).

As the use of other individual H_2RA is low (famotidine, nizatidine, roxatidine, ranitidine bismuth), the median cumulative DDD is not described in table 7 but is available in the ancillary documents

Table 7 Cumulative DDD for H_2RA class, ranitidine and cimetidine

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
H2 Class																		
Total	30,104	28	4 - 392	170,599	32	8 - 1,100	714,660	56	10 - 1,710	62,514	30	6 - 1,305	35,865	50	14 - 616	92,223	36	4 - 2,194
Age 0-18	1,447	10	2 - 50	6,804	10	5 - 100	69,769	15	5 - 131	7,651	15	2 - 80	3,564	28	14 - 93	2,387	21	2 - 129
Age 18-75	25,013	28	4 - 364	144,884	30	8 - 1,050	530,539	56	14 - 1,800	47,917	30	8 - 1,360	28,906	56	14 - 616	78,834	30	4 - 1,805
Age 75+	3,644	45	7 - 672	18,911	100	10 - 1,450	114,352	120	15 - 1,911	6,946	120	10 - 1,726	3,395	56	28 - 1,008	11,002	366	8 - 3,809
Inject	35	7	2 - 33	1,296	2	1 - 6	100	4	0 - 23	7	1	0 - 8	62	1	1 - 12	119	1	0 - 30
Oral	30,069	28	4 - 393	169,303	35	10 - 1,100	714,430	56	10 - 1,710	62,507	30	6 - 1,305	35,803	56	14 - 616	92,046	37	4 - 2,198
Unknown							130	15	0 - 300	0		-				58	11	0 - 96
Dur < 1 m	16,656	14	4 - 28	75,233	15	5 - 25	95,813	15	2 - 28	22,633	15	4 - 22	12,872	28	14 - 28	29,203	12	2 - 28
Dur 1-12 m	11,208	56	15 - 252	71,880	60	25 - 250	474,294	42	15 - 259	28,695	45	10 - 270	18,920	56	28 - 224	42,536	58	21 - 237
Dur 1-10 y	2,234	504	120 - 1,848	21,977	710	250 - 2,650	135,418	854	308 - 2,838	11,055	810	225 - 2,790	3,979	532	60 - 2,072	17,380	789	243 - 2,844
Dur > 10 y	6	2128	693 - 6,209	1,509	4100	2,000 - 7,744	9,135	4200	2,086 - 7,149	131	3780	1,852 - 6,885	94	2324	782 - 5,170	3,104	4125	1,918 - 7,451
Ranitidine																		
Total	26,083	28	4 - 420	150,513	35	6 - 1,100	615,360	56	10 - 1,684	60,075	30	6 - 1,260	35,865	50	14 - 616	90,692	35	4 - 2,190
Age 0-18	1,292	10	2 - 50	6,264	10	5 - 80	67,278	15	5 - 130	7,511	15	2 - 75	3,563	28	14 - 93	2,350	21	2 - 126
Age 18-75	21,640	28	4 - 378	126,350	30	6 - 1,073	447,666	58	15 - 1,800	45,980	30	8 - 1,320	28,905	56	14 - 616	77,677	30	4 - 1,793
Age 75+	3,151	50	7 - 714	17,899	100	10 - 1,450	100,416	120	15 - 1,904	6,584	105	10 - 1,699	3,397	56	28 - 1,008	10,665	370	8 - 3,880
Inject	35	7	2 - 33	919	1	1 - 6	94	4	0 - 21	7	1	0 - 8	62	1	1 - 12	120	1	0 - 29
Oral	26,048	28	4 - 420	149,594	35	10 - 1,100	615,266	56	10 - 1,684	60,068	30	6 - 1,260	35,803	56	14 - 616	90,517	36	4 - 2,194
Unknown										0		-				55	10	0 - 81
Dur < 1 m	14,637	14	4 - 28	67,175	20	5 - 25	72,909	15	3 - 28	22,225	15	4 - 22	12,883	28	14 - 28	28,715	12	2 - 28
Dur 1-12 m	9,528	57	15 - 252	62,582	60	25 - 260	419,393	30	10 - 258	27,509	45	10 - 270	18,918	56	28 - 224	42,068	58	21 - 237
Dur 1-10 y	1,913	522	161 - 1,890	19,456	725	250 - 2,700	115,776	868	322 - 2,850	10,228	810	225 - 2,790	3,970	532	60 - 2,072	16,841	790	247 - 2,848
Dur > 10 y	5	1904	633 - 5,914	1,300	4170	2,000 - 8,000	7,282	4242	2,130 - 7,136	113	3750	1,839 - 6,720	94	2324	782 - 5,170	3,068	4138	1,918 - 7,431
Cimetidine																		
Total	3,727	15	2 - 231	13,063	20	5 - 404	99,234	30	10 - 1,260	2,269	60	10 - 1,363	NA			201	15	0 - 610
Age 0-18	148	8	2 - 26	273	12	4 - 70	2,528	27	2 - 90	144	30	5 - 263				17	15	0 - 63
Age 18-75	3,137	15	2 - 206	12,299	20	5 - 400	82,310	30	10 - 1,218	1,799	60	10 - 1,413				151	15	0 - 569
Age 75+	442	28	4 - 334	491	30	2 - 700	14,396	84	14 - 1,522	326	135	11 - 1,508				33	84	0 - 702
Inject	0		-	443	2	2 - 8	8	15	3 - 67									-
Oral	3,727	15	2 - 231	12,620	20	5 - 425	99,097	30	10 - 1,262	2,269	60	10 - 1,363				193	15	0 - 625
Unknown							129	15	0 - 294	0		-				6	12	2 - 85

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
Dur < 1 m	2,003	8	2 - 28	6,705	10	3 - 25	23,420	15	0 - 28	600	15	5 - 30				74	3	0 - 16
Dur 1-12 m	1,478	38	8 - 168	5,338	50	12 - 200	59,736	42	22 - 240	1,119	70	15 - 300				91	22	8 - 118
Dur 1-10 y	245	315	50 - 1,172	960	512	158 - 1,875	15,286	780	260 - 2,640	545	720	226 - 2,697				36	416	94 - 2,164
Dur > 10 y			-	60	2912	1,328 - 5,898	792	3832	1,868 - 6,150	5	4050	2,751 - 5,610						

Total represents the number of users for whom info on DDD is available, Inject= Injectable thus for parenteral administration, med = median,
Dur=cumulative duration, NA= Information on cumulative DDD not available for Cimetidine for LPD Belgium

10.6. Cumulative dose in gram for H_2RA, ranitidine and other individual H_2RA

Table 8 describes the cumulative dose in gram per class and also per individual drug. The median cumulative dose of H_2RA was the lowest (8.4 gram) in DA_Germany and the highest in IMRD (18 gram). Similar results are observed when investigating ranitidine only with median cumulative dose ranging between 8.4 (DA_France)-16.8 (IMRD) gram. The median cumulative dose for cimetidine was higher (12 gram (DA_France) to 48 gram (IPCI) but of course the recommended daily dose is different for cimetidine (DDD = 0.8 gram) compared to ranitidine (DDD = 0.3 gram) which makes comparison of cumulative dose in mg less relevant.

The median cumulative dose in gram was comparable irrespective of the indication of use except for IMRD where the median cumulative dose in gram was higher for gastroduodenal/peptic ulcer. (ancillary tables)

For all databases and for both H_2RA as class, ranitidine and cimetidine, the median cumulative dose was the highest for oral administration (8.4 (DA_France) – 16.8 (IMRD and LPD_Belgium) gram for ranitidine) and also the highest in patients older than 75 years (15 (DA_France) – 111 (SIDIAP) gram for ranitidine). (table 8)

As can be expected, the median cumulative dose in gram increases by ICH exposure category.

As the use of other individual H_2RA is low (famotidine, nizatidine, roxatidine, ranitidine bismuth), the median cumulative dose in gram is not described in table 8 but is available in the ancillary tables.

Similar to table 8, table 9 describes the cumulative dose in gram per class and per individual drug but describes the number of users, P95 and the maximum values.

Table 8 Cumulative dose in grams for H_2RA, ranitidine and cimetidine

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
H2 Class																		
Total	30,104	8.4	1.1 - 126.0	170,599	9.0	1.5 - 322.0	714,660	18.0	3.2 - 580.5	62,514	9.0	1.8 - 405.0	35,865	15.0	4.2 - 184.8	92,223	10.2	1.2 - 647.4
Age 0-18	1,447	4.2	0.9 - 16.8	6,804	3.0	1.5 - 30.0	69,769	4.5	1.5 - 42.0	7,651	4.5	0.6 - 25.5	3,564	8.4	4.2 - 27.8	2,387	6.3	0.6 - 38.4
Age 18-75	25,013	8.4	1.1 - 119.7	144,884	9.0	1.5 - 315.0	530,539	18.0	4.5 - 613.2	47,917	9.0	2.2 - 432.0	28,906	16.8	4.2 - 184.8	78,834	9.0	1.2 - 529.2
Age 75+	3,644	16.8	2.1 - 226.8	18,911	30.0	3.0 - 426.0	114,352	43.8	4.5 - 655.2	6,946	36.0	3.0 - 533.2	3,395	16.8	8.4 - 302.4	11,002	109.8	2.1 - 1,135.2
Inject	35	2.1	0.5 - 10.0	1,296	0.5	0.2 - 4.0	100	1.3	0.0 - 12.0	7	0.3	0.0 - 2.5	62	0.2	0.2 - 3.5	119	0.3	0.0 - 8.9
Oral	30,069	8.4	1.1 - 126.2	169,303	10.0	1.5 - 330.0	714,430	18.0	3.5 - 580.8	62,507	9.0	1.8 - 405.0	35,803	16.8	4.2 - 184.8	92,046	10.2	1.2 - 648.6
Unknown							130	12.0	0.0 - 234.6	0		-				58	3.8	0.0 - 49.4
Dur < 1 m	16,656	4.2	1.1 - 12.0	75,233	4.0	0.8 - 8.0	95,813	6.0	0.8 - 22.4	22,633	4.5	1.1 - 8.4	12,872	8.4	4.2 - 8.4	29,203	3.6	0.6 - 8.4
Dur 1-12 m	11,208	18.0	4.5 - 81.0	71,880	18.0	4.5 - 82.5	474,294	16.8	4.5 - 90.0	28,695	13.5	3.0 - 90.0	18,920	16.8	8.4 - 67.2	42,536	17.4	6.3 - 70.8
Dur 1-10 y	2,234	159.6	34.2 - 613.4	21,977	210.0	60.0 - 824.2	135,418	286.8	99.0 - 991.0	11,055	243.0	58.5 - 891.0	3,979	159.6	17.9 - 621.6	17,380	229.8	60.9 - 846.6
Dur > 10 y	6	638.4	207.9 - 3,164.7	1,509	1230.0	222.4 - 2,685.6	9,135	1332.0	635.2 - 3,169.6	131	1134.0	283.5 - 2,864.2	94	697.2	234.6 - 1,551.0	3,104	1234.1	561.1 - 2,226.6
Ranitidine																		
Total	26,083	8.4	1.1 - 126.0	150,513	10.5	1.8 - 330.0	615,360	16.8	3.0 - 505.2	60,075	9.0	1.8 - 378.0	35,865	15.0	4.2 - 184.8	90,692	10.5	1.2 - 657.0
Age 0-18	1,292	3.1	0.8 - 15.0	6,264	3.0	1.5 - 24.0	67,278	4.5	1.5 - 39.0	7,511	4.5	0.6 - 22.5	3,563	8.4	4.2 - 27.8	2,350	6.3	0.6 - 37.9
Age 18-75	21,640	8.4	1.1 - 113.4	126,350	9.0	1.8 - 321.8	447,666	17.4	4.5 - 540.0	45,980	9.0	2.2 - 396.0	28,905	16.8	4.2 - 184.8	77,677	9.0	1.2 - 538.0
Age 75+	3,151	15.0	2.1 - 214.2	17,899	30.0	3.0 - 435.0	100,416	36.0	4.5 - 571.2	6,584	31.5	3.0 - 509.8	3,397	16.8	8.4 - 302.4	10,665	111.0	2.4 - 1,163.9
Inject	35	2.1	0.5 - 10.0	919	0.3	0.2 - 1.8	94	1.1	0.0 - 6.3	7	0.3	0.0 - 2.5	62	0.2	0.2 - 3.5	120	0.3	0.0 - 8.8
Oral	26,048	8.4	1.1 - 126.0	149,594	10.5	3.0 - 330.0	615,266	16.8	3.0 - 505.2	60,068	9.0	1.8 - 378.0	35,803	16.8	4.2 - 184.8	90,517	10.8	1.2 - 658.3
Unknown										0		-				55	3.0	0.0 - 24.3
Dur < 1 m	14,637	4.2	1.1 - 8.4	67,175	6.0	1.5 - 7.5	72,909	4.5	0.9 - 8.4	22,225	4.5	1.2 - 6.8	12,883	8.4	4.2 - 8.4	28,715	3.6	0.6 - 8.4
Dur 1-12 m	9,528	17.1	4.5 - 75.6	62,582	18.0	7.5 - 78.0	419,393	9.0	3.0 - 77.4	27,509	13.5	3.0 - 81.0	18,918	16.8	8.4 - 67.2	42,068	17.4	6.3 - 71.1
Dur 1-10 y	1,913	156.6	48.2 - 567.0	19,456	217.5	75.0 - 810.0	115,776	260.4	96.6 - 855.0	10,228	243.0	67.5 - 837.0	3,970	159.6	18.0 - 621.6	16,841	237.0	74.1 - 854.4
Dur > 10 y	5	571.2	189.8 - 1,774.1	1,300	1251.0	600.0 - 2,400.2	7,282	1272.5	639.0 - 2,140.7	113	1125.0	551.7 - 2,016.0	94	697.2	234.6 - 1,551.0	3,068	1241.4	575.4 - 2,229.4
Cimetidine																		
Total	3,727	12.0	2.0 - 184.8	13,063	16.0	4.0 - 323.6	99,234	24.0	8.0 - 1,008.0	2,269	48.0	8.0 - 1,090.6	NA			201	12.2	0.4 - 488.2
Age 0-18	148	6.0	2.0 - 20.9	273	10.0	2.8 - 56.0	2,528	21.3	2.0 - 72.0	144	24.0	4.0 - 210.6				17	12.2	0.4 - 50.7
Age 18-75	3,137	12.0	2.0 - 164.5	12,299	16.0	4.0 - 320.0	82,310	24.0	8.0 - 974.4	1,799	48.0	8.0 - 1,130.6				151	12.2	0.4 - 455.2
Age 75+	442	22.4	3.2 - 267.2	491	24.0	2.0 - 560.0	14,396	67.2	11.2 - 1,218.0	326	108.0	8.8 - 1,206.0				33	66.8	0.4 - 561.9
Inject	0		-	443	2.0	2.0 - 6.0	8	12.0	2.6 - 53.3									-
Oral	3,727	12.0	2.0 - 184.8	12,620	16.0	4.0 - 340.0	99,097	24.0	8.0 - 1,009.6	2,269	48.0	8.0 - 1,090.6				193	12.2	0.4 - 499.6
Unknown							129	12.0	0.0 - 235.2	0		-				6	9.2	1.4 - 68.0

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95	N	med	P5-P95
Dur < 1 m	2,003	6.0	2.0 - 22.4	6,705	8.0	2.3 - 20.0	23,420	12.0	0.4 - 22.4	600	12.0	4.0 - 24.0				74	2.1	0.4 - 12.8
Dur 1-12 m	1,478	30.0	6.0 - 134.4	5,338	40.0	10.0 - 160.0	59,736	33.6	18.0 - 192.0	1,119	56.0	12.0 - 240.0				91	18.0	6.2 - 94.8
Dur 1-10 y	245	252.0	40.3 - 937.4	960	410.0	126.0 - 1,500.0	15,286	624.0	208.4 - 2,112.0	545	576.0	181.2 - 2,157.6				36	333.2	75.5 - 1,731.4
Dur > 10 y			-	60	2330.0	1,062.7 - 4,718.2	792	3065.6	1,494.0 - 4,920.0	5	3240.0	2,200.6 - 4,488.0						

Total represents the number of users for whom info on dose is available, Inject= Injectable thus for parenteral administration, med = median,
Dur=cumulative duration; NA= Information on cumulative dose in grams not available for Cimetidine for LPD Belgium

Table 9 Cumulative dose in grams, P95 and maximum, for H_2RA, ranitidine and cimetidine

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	P95	maximum	N	P95	maximum	N	P95	maximum	N	P95	maximum	N	P95	maximum	N	P95	maximum
H2 Class																		
Total	30,104	126	3,539	170,599	322	7,616	714,660	580	38,907	62,514	405	5,065	35,865	185	2,353	92,223	647	4,742
Age 0-18	1,447	17	168	6,804	30	2,732	69,769	42	1,826	7,651	26	1,116	3,564	28	286	2,387	38	1,551
Age 18-75	25,013	120	3,539	144,884	315	7,616	530,539	613	38,907	47,917	432	5,065	28,906	185	2,353	78,834	529	4,742
Age 75+	3,644	227	1,361	18,911	426	3,040	114,352	655	9,302	6,946	533	2,496	3,395	302	1,080	11,002	1,135	4,651
Inject	35	10	13	1,296	4	500	100	12	72	7	3	3	62	3	8	119	9	45
Oral	30,069	126	3,539	169,303	330	7,616	714,430	581	38,907	62,507	405	5,065	35,803	185	2,353	92,046	649	4,742
Unknown							130	235	972							58	49	90
Dur < 1 m	16,656	12	92	75,233	8	90	95,813	22	67	22,633	8	1,296	12,872	8	360	29,203	8	209
Dur 1-12 m	11,208	81	582	71,880	83	536	474,294	90	1,502	28,695	90	657	18,920	67	459	42,536	71	1,350
Dur 1-10 y	2,234	613	2,755	21,977	824	3,537	135,418	991	38,165	11,055	891	4,617	3,979	622	1,579	17,380	847	3,944
Dur > 10 y	6	3,165	3,539	1,509	2,686	7,616	9,135	3,170	38,907	131	2,864	5,065	94	1,551	2,353	3,104	2,227	4,742
Ranitidine																		
Total	26,083	126	2,041	150,513	330	5,010	615,360	505	38,165	60,075	378	3,204	35,865	185	2,353	90,692	657	4,742
Age 0-18	1,292	15	168	6,264	24	2,730	67,278	39	1,584	7,511	22	1,116	3,563	28	286	2,350	38	1,551
Age 18-75	21,640	113	2,041	126,350	322	5,010	447,666	540	38,165	45,980	396	3,204	28,905	185	2,353	77,677	538	4,742
Age 75+	3,151	214	1,361	17,899	435	2,160	100,416	571	9,302	6,584	510	2,042	3,397	302	1,080	10,665	1,164	4,651
Inject	35	10	13	919	2	11	94	6	21	7	3	3	62	3	8	120	9	45
Oral	26,048	126	2,041	149,594	330	5,010	615,266	505	38,165	60,068	378	3,204	35,803	185	2,353	90,517	658	4,742
Unknown																55	24	90
Dur < 1 m	14,637	8	92	67,175	8	90	72,909	8	36	22,225	7	432	12,883	8	360	28,715	8	209
Dur 1-12 m	9,528	76	286	62,582	78	390	419,393	77	1,502	27,509	81	369	18,918	67	459	42,068	71	1,350
Dur 1-10 y	1,913	567	1,840	19,456	810	2,040	115,776	855	38,165	10,228	837	2,727	3,970	622	1,579	16,841	854	3,762
Dur > 10 y	5	1,774	2,041	1,300	2,400	5,010	7,282	2,141	31,575	113	2,016	3,204	94	1,551	2,353	3,068	2,229	4,742
Cimetidine																		
Total	3,727	185	3,539	13,063	324	7,616	99,234	1,008	38,892	2,269	1,091	4,871	NA			201	488	3,944
Age 0-18	148	21	62	273	56	1,292	2,528	72	1,817	144	211	648				17	51	55
Age 18-75	3,137	164	3,539	12,299	320	7,616	82,310	974	38,892	1,799	1,131	4,871				151	455	3,944
Age 75+	442	267	1,111	491	560	3,040	14,396	1,218	6,832	326	1,206	2,496				33	562	922
Inject				443	6	500	8	53	72									
Oral	3,727	185	3,539	12,620	340	7,616	99,097	1,010	38,892	2,269	1,091	4,871				193	500	3,944
Unknown							129	235	972							6	68	73
Dur < 1 m	2,003	22	45	6,705	20	104	23,420	22	256	600	24	1,296				74	13	22
Dur 1-12 m	1,478	134	582	5,338	160	536	59,736	192	582	1,119	240	648				91	95	289

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	P95	maximum	N	P95	maximum	N	P95	maximum	N	P95	maximum	N	P95	maximum	N	P95	maximum
Dur 1-10 y	245	937	2,755	960	1,500	3,528	15,286	2,112	26,178	545	2,158	4,871				36	1,731	3,944
Dur > 10 y				60	4,718	7,616	792	4,920	38,892	5	4,488	4,788						

Total represents the number of users for whom info on dose is available, Inject= Injectable thus for parenteral administration, med = median,
Dur=cumulative duration, NA= Information on cumulative dose in grams not available for Cimetidine for LPD Belgium

10.7. Cumulative dose in gram for ranitidine by ICH duration

Table 10 describes the cumulative dose in gram for ranitidine by the different ICH exposure categories.

Similar to what was already reported in table 5, the number of patients with a cumulative duration between 1-10 years was low and this number further dropped when investigating cumulative use of ranitidine of more than 10 years.

As ICH strata are based on cumulative exposure by itself, the median cumulative dose of ranitidine was the highest for a ranitidine exposure of more than 10 years.

For all ICH categories, no obvious difference in median cumulative dose by indication of use could be observed (see ancillary tables). The effect of age – with highest use in patients older than 75 years – was present in all ICH exposure categories. Also, in patient exposed to ranitidine between 1-12 months, the median cumulative dose was higher in patients older than 75 years compared to patients aged 18-75 years except for LPD_Belgium and SIDIAP.

Table 10 Cumulative dose in grams for ranitidine by ICH category and age group

		DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
ICH category	Age	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95
0-1 M	0-18	1,039	2.2	0.8 - 8.4	4,723	3.0	1.5 - 6.0	4,824	4.2	1.1 - 8.4	2,789	2.2	0.4 - 4.5	1,221	8.4	4.2 - 8.4	1,249	3.3	0.6 - 6.9
	18-75	12,548	4.2	1.1 - 8.4	58,344	6.0	1.5 - 7.5	58,399	4.5	0.9 - 8.4	18,049	4.5	1.5 - 7.5	10,965	8.4	4.2 - 8.4	26,101	3.6	0.6 - 8.4
	75+	1,050	4.2	1.1 - 8.4	4,108	6.0	1.5 - 7.5	9,686	4.5	0.9 - 8.4	1,387	4.5	1.1 - 8.7	697	8.4	4.2 - 8.4	1,365	3.3	0.6 - 8.4
	Overall age group	14,637	4.2	1.1 - 8.4	67,175	6.0	1.5 - 7.5	72,909	4.5	0.9 - 8.4	22,225	4.5	1.2 - 6.8	12,883	8.4	4.2 - 8.4	28,715	3.6	0.6 - 8.4
1-12 M	0-18	246	9.0	2.8 - 25.2	1,479	12.0	6.0 - 45.0	59,602	4.5	1.5 - 27.0	4,368	4.5	1.4 - 22.5	2,226	8.4	8.4 - 33.6	1,026	9.0	4.8 - 36.6
	18-75	7,676	16.8	4.5 - 75.6	51,841	18.0	7.5 - 75.0	302,163	13.5	9.0 - 78.6	20,095	16.5	6.6 - 84.2	14,695	16.8	8.4 - 67.2	37,731	17.4	6.3 - 68.4
	75+	1,606	25.2	4.5 - 79.8	9,262	30.0	7.5 - 90.0	57,628	18.0	9.0 - 92.4	3,046	22.5	4.5 - 108.0	1,997	16.8	8.4 - 84.0	3,311	19.8	6.3 - 90.2
	Overall age group	9,528	17.1	4.5 - 75.6	62,582	18.0	7.5 - 78.0	419,393	9.0	3.0 - 77.4	27,509	13.5	3.0 - 81.0	18,918	16.8	8.4 - 67.2	42,068	17.4	6.3 - 71.1
1-10 Y	0-18	7	50.4	32.5 - 163.0	60	177.8	67.3 - 568.6	2,819	72.0	19.5 - 436.8	353	21.0	7.5 - 204.8	116	25.2	16.8 - 142.7	70	202.9	58.1 - 566.5
	18-75	1,413	159.6	48.5 - 579.6	14,970	225.0	75.0 - 825.8	80,780	270.0	111.0 - 882.0	7,736	252.0	90.0 - 860.2	3,156	168.0	30.0 - 639.3	11,714	229.8	72.0 - 842.6
	75+	493	151.2	50.4 - 505.8	4,426	210.0	75.0 - 720.0	32,177	246.6	101.1 - 779.4	2,139	229.5	76.5 - 777.7	698	161.7	33.6 - 571.6	5,057	258.6	81.5 - 877.8
	Overall age group	1,913	156.6	48.2 - 567.0	19,456	217.5	75.0 - 810.0	115,776	260.4	96.6 - 855.0	10,228	243.0	67.5 - 837.0	3,970	159.6	18.0 - 621.6	16,841	237.0	74.1 - 854.4
1>10 Y	0-18				<5		-	33	909.0	493 - 1,498	<5		-				5	1218	770 - 1,509
	18-75	3	571	488 - 1,894	1,195	1260	610 - 2,451	6,324	1291	657 - 2,182	100	1132	558 - 2,045	89	706	239 - 1,566	2,131	1255	574 - 2,247
	75+	<5		-	103	1146	571 - 1,704	925	1188	585 - 1,793	12	1107	272 - 1,338	5	655	254 - 1,005	932	1214	581 - 2,174
	Overall age group	5	571	190 - 1,774	1,300	1251	600 - 2,400	7,282	1273	639 - 2,141	113	1125	552 - 2,016	94	697	235 - 1,551	3,068	1241	575 - 2,229

Total represents the number of users for whom info on dose is available, Med = median, the sum of the number of users of the overall age groups is lower than the total number of users of ranitidine as information on dosing is not available for all ranitidine users

10.8. Cumulative annual dose for H_2RA, ranitidine and other individual H_2RA

To control for differences in observation time, the cumulative annual dose was calculated which is the cumulative dose divided by the person time. Results of the cumulative annual dose are described in table 11.

The median cumulative annual dose of H_2RA as class ranged between 1.4 g (DA_Germany) and 2.4g (DA_France). The median cumulative annual dose was lowest in children < 18 years, increased with age and was the highest in individuals older than 75 years (range 3.6 g (LPD_Belgium) – 10.5 g (SIDIAP)).

The median cumulative annual dose of ranitidine in gram per year ranged between 1.5 g (DA_Germany) and 2.3 g (LPD Belgium and DA_France). The median cumulative annual dose was lowest in children < 18 years, increased with age and was the highest in individuals older than 75 years (range 3.6 g (LPD_Belgium) – 11.8 g (SIDIAP)).

The median cumulative annual dose of cimetidine in milligram per year ranged between 1.0 g (SIDIAP) and 10.3 g (IPCI). Similar trends with regard to increasing annual dose per age was observed.

In all databases, the median cumulative annual dose was much lower for parenteral use compared to oral use, but the number of patients with parenteral use was low.

As the use of other individual H_2RA is low (famotidine, nizatidine, roxatidine, ranitidine bismuth), the cumulative dose in gram is not described in table 10 but is available in the ancillary documents.

Table 11 Cumulative annual dose in g/year for H_2RA, ranitidine and cimetidine

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95
H2 Class																		
Total	30,104	2.4	0.2 - 71.4	166,405	1.4	0.1 - 65.5	714,660	2.3	0.3 - 84.5	62,514	2.1	0.3 - 91.7	35,865	2.3	0.5 - 55.3	92,187	1.2	0.1 - 64.0
Age 0-18	1,447	0.9	0.1 - 42.9	6,612	0.6	0.1 - 11.0	69,769	1.0	0.2 - 13.8	7,651	1.0	0.2 - 10.3	3,564	1.7	0.5 - 28.4	2,387	0.5	0.0 - 4.5
Age 18-75	25,013	2.3	0.2 - 70.5	141,220	1.3	0.1 - 61.3	530,539	2.2	0.4 - 74.0	47,917	2.1	0.4 - 91.8	28,906	2.3	0.5 - 55.8	78,807	0.9	0.1 - 49.9
Age 75+	3,644	5.7	0.4 - 83.5	18,573	4.0	0.2 - 97.8	114,352	8.0	0.5 - 114.1	6,946	9.0	0.5 - 114.8	3,395	3.6	0.5 - 61.3	10,993	10.5	0.2 - 120.4
Inject	35	0.8	0.2 - 12.9	1,280	0.1	0.0 - 2.5	100	0.2	0.0 - 11.0	7	0.1	0.0 - 0.7	62	0.1	0.0 - 4.5	119	0.0	0.0 - 1.3
Oral	30,069	2.4	0.2 - 71.5	165,125	1.4	0.1 - 65.9	714,430	2.3	0.3 - 84.5	62,507	2.1	0.3 - 91.7	35,803	2.3	0.5 - 55.3	92,010	1.2	0.1 - 64.1
Unknown							130	1.0	0.0 - 40.4	0		-				58	0.3	0.0 - 7.1
Dur < 1 m	16,656	1.1	0.2 - 56.8	71,977	0.4	0.1 - 11.5	95,813	0.6	0.1 - 5.2	22,633	0.7	0.2 - 3.0	12,872	1.1	0.4 - 55.8	29,181	0.3	0.0 - 0.9
Dur 1-12 m	11,208	5.0	0.7 - 56.7	70,953	2.2	0.3 - 41.1	474,294	1.8	0.4 - 25.6	28,695	3.0	0.6 - 32.4	18,920	2.8	0.7 - 33.9	42,525	1.3	0.5 - 7.7
Dur 1-10 y	2,234	33.2	5.9 - 110.4	21,966	23.1	3.8 - 106.8	135,418	33.8	7.6 - 119.7	11,055	51.9	10.3 - 165.6	3,979	19.5	2.4 - 84.2	17,377	21.6	5.1 - 86.7
Dur > 10 y	6	72.0	38.7 - 335.0	1,509	76.7	15.2 - 201.5	9,135	92.9	45.9 - 215.9	131	115.9	40.9 - 408.5	94	63.9	16.5 - 156.5	3,104	101.7	44.3 - 196.9
Ranitidine																		
Total	26,083	2.3	0.2 - 66.7	146,900	1.5	0.1 - 65.8	615,360	2.0	0.3 - 74.0	60,075	1.9	0.3 - 86.6	35,865	2.3	0.5 - 55.3	90,657	1.2	0.1 - 64.9
Age 0-18	1,292	0.9	0.1 - 40.1	6,085	0.6	0.1 - 10.4	67,278	1.0	0.2 - 13.8	7,511	1.0	0.2 - 9.6	3,563	1.7	0.5 - 28.4	2,350	0.5	0.1 - 4.6
Age 18-75	21,640	2.1	0.2 - 64.1	123,221	1.3	0.1 - 61.0	447,666	1.9	0.4 - 65.7	45,980	2.0	0.4 - 86.5	28,905	2.3	0.5 - 55.8	77,651	1.0	0.1 - 50.6
Age 75+	3,151	5.6	0.4 - 80.0	17,594	4.2	0.3 - 98.1	100,416	6.6	0.5 - 106.7	6,584	8.3	0.5 - 111.2	3,397	3.6	0.5 - 61.3	10,656	11.8	0.2 - 122.6
Inject	35	0.8	0.2 - 12.9	906	0.1	0.0 - 3.0	94	0.2	0.0 - 11.1	7	0.1	0.0 - 0.7	62	0.1	0.0 - 4.5	120	0.0	0.0 - 1.2
Oral	26,048	2.3	0.2 - 66.8	145,994	1.5	0.2 - 66.0	615,266	2.0	0.3 - 74.1	60,068	1.9	0.3 - 86.6	35,803	2.3	0.5 - 55.3	90,482	1.2	0.1 - 65.0
Unknown										0		-				55	0.2	0.0 - 3.3
Dur < 1 m	14,637	1.0	0.2 - 56.8	64,374	0.4	0.1 - 10.1	72,909	0.5	0.1 - 3.9	22,225	0.7	0.2 - 2.7	12,883	1.1	0.4 - 55.6	28,693	0.3	0.0 - 0.9
Dur 1-12 m	9,528	4.9	0.8 - 56.7	61,781	2.4	0.5 - 41.5	419,393	1.6	0.4 - 21.1	27,509	2.9	0.6 - 30.0	18,918	2.8	0.7 - 33.9	42,058	1.3	0.5 - 7.7
Dur 1-10 y	1,913	32.5	7.0 - 106.7	19,445	24.7	5.4 - 106.1	115,776	30.4	7.4 - 108.5	10,228	51.3	11.7 - 148.0	3,970	19.6	2.4 - 84.2	16,838	22.5	6.4 - 87.7
Dur > 10 y	5	63.5	37.4 - 208.7	1,300	79.0	33.5 - 193.4	7,282	87.4	46.3 - 145.8	113	113.4	52.4 - 254.7	94	63.9	16.5 - 156.5	3,068	102.8	46.7 - 197.2
Cimetidine																		
Total	3,727	4.0	0.5 - 91.2	12,829	1.9	0.3 - 79.0	99,234	3.5	0.5 - 137.4	2,269	10.3	1.1 - 231.4	NA			201	1.0	0.0 - 52.9
Age 0-18	148	1.9	0.4 - 57.2	269	1.1	0.2 - 25.7	2,528	1.4	0.2 - 13.4	144	4.1	0.6 - 25.8				17	1.0	0.0 - 3.9
Age 18-75	3,137	3.9	0.5 - 90.9	12,080	1.9	0.3 - 77.0	82,310	3.1	0.5 - 112.8	1,799	9.6	1.2 - 231.9				151	0.9	0.0 - 38.4
Age 75+	442	6.4	0.8 - 95.4	480	3.6	0.2 - 131.8	14,396	12.9	0.9 - 235.9	326	30.0	1.3 - 270.8				33	6.2	0.1 - 100.7
Inject	0		-	441	0.3	0.1 - 1.9	8	2.9	0.6 - 8.1									-
Oral	3,727	4.0	0.5 - 91.2	12,388	2.0	0.3 - 81.2	99,097	3.5	0.5 - 137.5	2,269	10.3	1.1 - 231.4				193	1.0	0.0 - 53.8
Unknown							129	1.2	0.0 - 40.5	0		-				6	0.8	0.1 - 7.2
Dur < 1 m	2,003	1.9	0.4 - 75.7	6,528	0.8	0.2 - 22.3	23,420	1.1	0.0 - 8.1	600	1.9	0.6 - 7.6				74	0.2	0.0 - 1.0
Dur 1-12 m	1,478	7.0	1.2 - 75.7	5,281	3.5	0.7 - 54.7	59,736	3.5	1.1 - 44.1	1,119	10.6	2.3 - 80.1				91	1.4	0.5 - 8.0

	DA-France			DA-Germany			IMRD			IPCI			LPD-Belgium			SIDIAP		
	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95	N	Med	P5-P95
Dur 1-10 y	245	48.3	5.3 - 167.8	960	38.2	7.9 - 175.7	15,286	70.5	17.2 - 263.4	545	105.1	35.0 - 358.3				36	33.7	7.7 - 321.3
Dur > 10 y			-	60	149.2	57.6 - 383.4	792	187.0	86.7 - 351.6	5	305.0	179.9 - 479.4						

Total represents the number of users for whom info on dose is available, Inject= Injectable thus for parenteral administration, med = median,
Dur=cumulative duration, NA= Information on dosing not available for Cimetidine for LPD Belgium

10.9. Indication of use of H_2RA, ranitidine and other individual H_2RA

The indication of use was investigated by checking the presence of conditions prior to the first prescription of H_2RA. The indication of use was investigated in the past 6 months (180 days) and in the past 12 months (365 days) of the first prescription of the H_2RA during follow-up.

The proportion of patients for whom the indication of use is unknown (= patients without a disease code of gastric/duodenal ulcer, GERD or Zollinger Ellison in the 1 year prior to treatment initiation) was high and ranged between 71.9% (LPD_Belgium) and 97.3% (SIDIAP) for H_2RA. (table 12) For those patients with an indication of use, the majority was for reflux disease (67.1% (DA_Germany)-94.4% (LPD-Belgium)). For gastric/duodenal ulcer, these proportions ranged between 5.6% (LPD_Belgium) – 32.9% (DA_Germany)). Very few patients were prescribed H_2RA for reason of Zollinger-Ellison – in fact, Zollinger Ellison was only reported in IMRD.

Similar results were found when investigating ranitidine and the other H_2RA. In DA_Germany, the indication of use for cimetidine and nizatidine was more often for ulcer than for GERD.

Table 12 Indication of use for H_2RA, ranitidine and other individual H_2RA assessed in the 12 months prior to the first prescription

Ingredient		DA-FRANCE	DA-GERMANY	IMRD	IPCI	LPD-BELGIUM	SIDIAP	Total
H2 Class	Total	36,826	170,600	714,828	63,594	53,206	96,663	1,135,717
	GERD	3,079 (93.36)	25,482 (67.11)	53,025 (93.24)	5,249 (90.08)	14,292 (94.4)	2,117 (81.77)	103,244 (84.84)
	ULCER	219 (6.64)	12,488 (32.89)	3,840 (6.75)	578 (9.92)	848 (5.6)	472 (18.23)	18,445 (15.16)
	Zollinger-Ellison			7 (0.01)				7 (0.01)
	Unknown	33,550 (91.1)	134,060 (78.58)	658,257 (92.09)	57,794 (90.88)	38,265 (71.92)	94,088 (97.34)	1,016,014 (89.46)
Ranitidine	Total	31,613	150,513	615,485	61,063	52,683	94,962	1,006,319
	GERD	2,717 (93.27)	23,447 (71.14)	48,151 (93.75)	5,158 (90.55)	14,210 (94.44)	2,092 (82.43)	95,775 (86.66)
	ULCER	196 (6.73)	9,514 (28.86)	3,204 (6.24)	538 (9.45)	837 (5.56)	446 (17.57)	14,735 (13.33)
	Zollinger-Ellison			7 (0.01)				7 (0.01)
	Unknown	28,720 (90.85)	118,884 (78.99)	564,418 (91.7)	55,393 (90.71)	37,832 (71.81)	92,438 (97.34)	897,685 (89.2)
Cimetidine	Total	4,989	13,063	99,287	2,364	642	275	120,620
	GERD	376 (94)	1,255 (32.62)	6,147 (89.58)	93 (66.43)	136 (90.67)		8,007 (70.24)
	ULCER	24 (6)	2,592 (67.38)	715 (10.42)	47 (33.57)	14 (9.33)		3,392 (29.76)
	Unknown	4,591 (92.02)	9,365 (71.69)	92,465 (93.13)	2,225 (94.12)	497 (77.41)	272 (98.91)	109,415 (90.71)
Nizatidine	Total	84	3,010	35,234	71			38,399
	GERD	8 (100)	337 (27)	2,346 (88.73)	6 (100)			2,697 (69.05)
	ULCER	0 (0)	911 (73)	298 (11.27)	0 (0)			1,209 (30.95)
	Unknown	74 (88.1)	1,818 (60.4)	32,615 (92.57)	63 (88.73)			34,570 (90.03)
Famotidine	Total	658	13,254	2,257	704		2,092	18,965
	GERD	47 (100)	2,405 (63.34)	207 (88.84)	34 (79.07)		47 (64.38)	2,740 (65.35)
	ULCER	0 (0)	1,392 (36.66)	26 (11.16)	9 (20.93)		26 (35.62)	1,453 (34.65)
	Unknown	609 (92.55)	9,595 (72.39)	2,027 (89.81)	661 (93.89)		2,020 (96.56)	14,912 (78.63)
Roxatidine	Total		1,122					1,130
	GERD		115 (27.71)					115 (27.71)
	ULCER		300 (72.29)					300 (72.29)
	Unknown		727 (64.8)					735 (65.04)
Ranitidine bismuth	Total			460			36	496
	GERD			49 (52.13)				49 (52.13)
	ULCER			45 (47.87)				45 (47.87)

Ingredient	DA-FRANCE	DA-GERMANY	IMRD	IPCI	LPD-BELGIUM	SIDIAP	Total
Unknown			367 (79.78)			32 (88.89)	399 (80.44)

GERD= gastro-esophageal relux disease

10.10. History of renal impairment in patients treated with H_2RA, ranitidine and other individual H_2RA

As NDMA toxicity might be aggravated in patients with chronic renal failure, the presence of chronic renal impairment during exposure to H_2RA was also investigated. The presence of chronic renal impairment in patients using H_2RA was investigated for the presence of Condition concepts in the 365 days prior to the first H_2-receptor antagonist prescription.

As can be observed from table 13, in all databases, the number of patients with renal impairment was low and for H_2RA ranged between 0.3% (DA_France) to 1.8% (DA_Germany). Similar results were observed for ranitidine and the other H_2RA.

Table 13 Number of patients with history of renal impairment

	DA-FRANCE	DA-GERMANY	IMRD	IPCI	LPD-BELGIUM	SIDIAP	Total
H2 Class (total number of users)	36,826	170,600	714,828	63,594	53,206	96,663	1,135,717
Renal impairment N (%)	95 (0.26)	3,079 (1.80)	9,104 (1.27)	753 (1.18)	208 (0.39)	677 (0.70)	13,916 (1.23)
Ranitidine (total number of users)	31,613	150,513	615,485	61,063	52,683	94,962	1,006,319
Renal impairment N (%)	89 (0.28)	2,876 (1.91)	9,194 (1.49)	742 (1.22)	206 (0.39)	660 (0.70)	13,767 (1.37)
Cimetidine (total number of users)	4,989	13,063	99,287	2,364	642		120,345
Renal impairment N (%)	8 (0.16)	151 (1.16)	418 (0.42)	14 (0.59)	2 (0.31)		593 (0.49)
Nizatidine (total number of users)		3,010	35,234				38,244
Renal impairment N (%)		31 (1.03)	126 (0.36)				157 (0.41)
Famotidine (total number of users)	658	13,254	2,257	704		2,092	18,965
Renal impairment N (%)	2 (0.30)	166 (1.25)	30 (1.33)	10 (1.42)		27 (1.29)	235 (1.24)
Roxatidine (total number of users)		1,122					1,122
Renal impairment N (%)		11 (0.98)					11 (0.98)
Ranitidine bismuth citrate (total number of users)			460				460
Renal impairment N (%)			1 (0.22)				1 (0.22)

11 Discussion

Key results

The incidence of ranitidine was low and ranged between 0.7/1,000 to 11.4/1,000 over all databases and over all calendar years. The incidence was higher in females than in males and decreased over calendar time in DA_Germany, IPCI and LPD_Belgium but in all databases remained stable over the last 5 years. Less than 3% of patients used ranitidine with prevalences ranging between 1.0 and 28.3/1,000. Similar finding with regard to change over calendar time and difference by gender were observed as for the incidence of ranitidine. In all databases, ranitidine use increased with age from the age of 20 years on and was the highest in patients aged 70-90 years.

Ranitidine was mainly prescribed and/or dispensed via oral formulation and use of parenteral ranitidine was less than 2% in all databases.

The proportion of patients using ranitidine for a duration between 1-10 years was low and ranged between 6.5-18.8%. Use of ranitidine for more than 10 years was less than 4%.

For the six databases, the median cumulative duration of ranitidine ranged between 28 to 60 days with a median cumulative dose ranging between 8.4 and 16.8 gram. The median cumulative duration and median cumulative exposure were the highest in individuals older than 75 years.

In all databases, the median PDD/DDD ratio for ranitidine was around 1 implying that the patient was prescribed ranitidine in agreement with the dose recommendations from the WHO.

Of the patients with an indication of use, the majority used ranitidine for reflux disease (range over databases 71-94%). The patients with a medical history of chronic renal impairment was low (less than 2%) but potentially underrepresented.

Interpretation

In this study we report a low use of ranitidine (and other H_2RA) with a decrease over calendar time which was mainly obvious in DA_Germany, IPCI and LPD_Belgium. In all databases, use stabilized over the last 5 years. Although unfortunately, there were very few articles describing use patterns of ranitidine and other H_2RA, other research groups also reported on a decrease of H_2RA in favor of proton pump inhibitors (PPI) as these are considered to be more effective than H_2RA in both preventing and healing ulcers. (Kurdi, Leporowski et al. 2018).

Few publications allowed us to benchmark our data on the treatment patterns of ranitidine (and other H_2RA) to the results of other research groups. It proofed to be difficult to compare our data on the incidence and prevalence of ranitidine to results from other research groups. Martin et al, investigated trends in prescribing PPI and H_2RA in primary care by means of a postal survey sent to 250 primary care physicians from the UK during the study period 1991-1996. They not only reported a sharp increase in use of PPI at the expense of H_2RA. They also described that H_2RA was more often discontinued – compared to PPI – because of treatment failure.(Martin, Lim et al. 1998)

Less than 1 patient in 5 used ranitidine for a cumulative duration between 1-10 years and less than 4% of patients used ranitidine for more than 10 years. The Summary of Product Characteristics (SPC) of ranitidine only recommends maintenance therapy with ranitidine for the treatment of Duodenal ulcers associated with Helicobacter pylori infection, Zollinger-Ellison Syndrome and healed oesophagitis. Whether criteria for maintenance therapy were met is difficult to investigate as the indication of use was often missing within the database.

Limitations of the research methods

For this study, real world data from electronic healthcare records was used. There might exist differences between the databases with regard to availability of certain data.

First, conditions which determine the indication of use of H_2RA as well as conditions for the comorbidity renal impairment might be underreported in the source databases. This is also what was observed as the indication of use was unknown in 71.9% to 97.3% of the population. Similarly also

chronic impairment was underreported as we know from previous research that up to 7% of the population has a diagnosis of chronic kidney injury. (van Blijderveen, Straus et al. 2014) We probably underreported chronic kidney impairment as we only considered disease codes and no kidney function (glomerular filtration rate).

Second, as low dose ranitidine is also available as an over the counter (OTC) drug, there is the potential of underreporting of ranitidine use. In contrast, as prescription and dispensing data were used, we might have overestimated the use of ranitidine and other H_2RA, as the actual drug intake might have been lower.

Third, as primary care databases were used, use of H_2RA in the hospital setting is lacking.

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

Strengths and Generalisability

Generalisability of our findings is high as we used real life data to investigate treatment patterns of ranitidine and other H_2RA. The strength of our study is the fact that we used a large dataset 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 consulted in the web application. Although there are some country specific differences in the incidence and prevalence of ranitidine and other H_2RA there are numerous consistent findings with regard to the low proportion of patients with long term use, a median PDD/DDD ratio of 1, more use in females than in males, highest use in patients older than 75 years and GERD as main indication for ranitidine use.

12 Conclusions

Amongst the H_2RA, mainly ranitidine was used but with low incidence numbers (less than 3% initiate treatment) and country specific differences. Less than 3% of patients are treated with ranitidine with the highest use in females and in the elderly. A decrease in incidence and prevalence over calendar time has been observed, although not in all databases, but use has been stabilized over the past 5 years.

The proportion of patients using ranitidine for more than 10 years was less than 5% implying that the median cumulative duration and median cumulative exposure is low.

13 References

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Annex 1. List of stand-alone documents

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

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

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

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	Page 12
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

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

Annex 3. DRUG_STRENGTH table

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

The DRUG_STRENGTH table contains the following relevant fields:

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

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

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

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

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

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

Annex 4. Concept Sets

This Annex provides an overview of the standard concepts that were present in each database for the indications and Chronic Renal Impairment. For the condition domain these refer to SNOMED codes. In addition, the sources codes that were included through the code mapping from source to standard concept are presented. The counts show the total number of records that were found with this code. A patient can have multiple codes over time, and codes can refer to the same record occurrence through the vocabulary hierarchy.

1. DA-FRANCE

1.1. GERD

Table 1.1.1 Included standard concepts in DA-FRANCE for GERD

standard_concept_id	concept_name	n
4144111	Gastroesophageal reflux disease without esophagitis	140372
30437	Gastro-esophageal reflux disease with esophagitis	2461

Table 1.1.2 Included source concepts in DA-FRANCE for GERD

source_concept_code	source_concept_name	source_vocabulary_id	n
K21.9	Gastro-oesophageal reflux disease without oesophagitis	ICD10	140372
K21.0	Gastro-oesophageal reflux disease with oesophagitis	ICD10	2461

1.2. Gastric Or Duodenal Ulcer

Table 1.2.1 Included standard concepts in DA-FRANCE for Ulcer

standard_concept_id	concept_name	n
4248429	Gastric ulcer without hemorrhage AND without perforation	5315
4291028	Peptic ulcer without hemorrhage AND without perforation	2034
4209746	Duodenal ulcer without hemorrhage AND without perforation	1414
25844	Ulcer of esophagus	241
4211001	Chronic gastric ulcer with hemorrhage	130
4150681	Chronic gastric ulcer with perforation	77
4101104	Gastrojejunal ulcer without hemorrhage AND without perforation	31
4222896	Chronic duodenal ulcer without hemorrhage AND without perforation	30
4232181	Chronic duodenal ulcer with hemorrhage	29
4173408	Chronic duodenal ulcer with perforation	13
4174044	Chronic peptic ulcer with hemorrhage	11
4289830	Chronic duodenal ulcer with hemorrhage AND perforation	0
4296611	Chronic gastric ulcer without hemorrhage AND without perforation	0

Table 1.2.2 Included source concepts in DA-FRANCE for Ulcer

source_concept_code	source_concept_name	source_vocabulary_id	n
K25.9	Gastric ulcer, Unspecified as acute or chronic, without haemorrhage or perforation	ICD10	5315
K27.9	Peptic ulcer, site unspecified, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	2034

source_concept_code	source_concept_name	source_vocabulary_id	n
K26.9	Duodenal ulcer, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	1414
K22.1	Ulcer of oesophagus	ICD10	241
K25.4	Gastric ulcer, Chronic or unspecified with haemorrhage	ICD10	130
K25.5	Gastric ulcer, Chronic or unspecified with perforation	ICD10	77
K28.9	Gastrojejunal ulcer, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	31
K26.7	Duodenal ulcer, chronic without haemorrhage or perforation	ICD10	30
K26.4	Duodenal ulcer, chronic or unspecified with haemorrhage	ICD10	29
K26.5	Duodenal ulcer, chronic or unspecified with perforation	ICD10	13
K27.4	Peptic ulcer, site unspecified, chronic or unspecified with haemorrhage	ICD10	11
K25.7	Gastric ulcer, Chronic without haemorrhage or perforation	ICD10	0
K26.6	Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation	ICD10	0

1.3. Chronic Renal Impairment

Table 1.3.1 Included standard concepts in DA-FRANCE for CRI

standard_concept_id	concept_name	n
192359	Renal failure syndrome	12217
46271022	Chronic kidney disease	6895
443919	Hypertensive renal failure	993
201313	Hypertensive renal disease	484
195556	Hypertensive heart AND renal disease	229
4170452	Postoperative renal failure	73
196455	Hepatorenal syndrome	46
193519	Impaired renal function disorder	0
443597	Chronic kidney disease stage 3	0

Table 1.3.2 Included source concepts in DA-FRANCE for CRI

source_concept_code	source_concept_name	source_vocabulary_id	n
N19	Unspecified kidney failure	ICD10	12217
N18.9	Chronic kidney disease, unspecified	ICD10	6895
I12.0	Hypertensive renal disease with renal failure	ICD10	993
I12.9	Hypertensive renal disease without renal failure	ICD10	484
I13.9	Hypertensive heart and renal disease, unspecified	ICD10	229
N99.0	Postprocedural renal failure	ICD10	73
K76.7	Hepatorenal syndrome	ICD10	46
N18.3	Chronic kidney disease, stage 3	ICD10	0
N25.8	Other disorders resulting from impaired renal tubular function	ICD10	0

2. DA-GERMANY

2.1. GERD

Table 2.1.1 Included standard concepts in DA-GERMANY for GERD

standard_concept_id	concept_name	n
30437	Gastro-esophageal reflux disease with esophagitis	702427
4144111	Gastroesophageal reflux disease without esophagitis	455011

Table 2.1.2 Included source concepts in DA-GERMANY for GERD

source_concept_code	source_concept_name	source_vocabulary_id	n
K21.0	Gastro-oesophageal reflux disease with oesophagitis	ICD10	702427
K21.9	Gastro-oesophageal reflux disease without oesophagitis	ICD10	455011

2.2. Gastric Or Duodenal Ulcer

Table 2.2.1 Included standard concepts in DA-GERMANY for Ulcer

standard_concept_id	concept_name	n
4248429	Gastric ulcer without hemorrhage AND without perforation	102227
4209746	Duodenal ulcer without hemorrhage AND without perforation	67248
4195231	Acute gastric ulcer without hemorrhage AND without perforation	13627
4291028	Peptic ulcer without hemorrhage AND without perforation	10968
25844	Ulcer of esophagus	9338
4138962	Acute duodenal ulcer without hemorrhage AND without perforation	8099
4231580	Acute gastric ulcer with hemorrhage	5557
4296611	Chronic gastric ulcer without hemorrhage AND without perforation	5549
4211001	Chronic gastric ulcer with hemorrhage	4028
4222896	Chronic duodenal ulcer without hemorrhage AND without perforation	3565
4027729	Acute duodenal ulcer with hemorrhage	2541
4150681	Chronic gastric ulcer with perforation	2254
4101104	Gastrojejunal ulcer without hemorrhage AND without perforation	1951
4232181	Chronic duodenal ulcer with hemorrhage	1711
4057953	Acute gastric ulcer with perforation	636
4174044	Chronic peptic ulcer with hemorrhage	603
4169592	Acute gastric ulcer with hemorrhage AND perforation	490
4173408	Chronic duodenal ulcer with perforation	419
4204555	Chronic peptic ulcer without hemorrhage AND without perforation	385
4146517	Chronic peptic ulcer with perforation	328
4163865	Acute peptic ulcer without hemorrhage AND without perforation	326
4265479	Acute duodenal ulcer with perforation	247
4177387	Chronic gastrojejunal ulcer without hemorrhage AND without perforation	234
4336230	Acute duodenal ulcer with hemorrhage AND perforation	216
4294973	Chronic gastric ulcer with hemorrhage AND with perforation	191
4046500	Acute peptic ulcer with hemorrhage	167
4147683	Acute gastrojejunal ulcer without hemorrhage AND without perforation	146

standard_concept_id	concept_name	n
4194543	Acute peptic ulcer with perforation	105
4289830	Chronic duodenal ulcer with hemorrhage AND perforation	104
433515	Chronic gastrojejunal ulcer with hemorrhage	85
4274491	Acute gastrojejunal ulcer with hemorrhage	53
4217947	Acute gastrojejunal ulcer with hemorrhage AND perforation	50
4247008	Chronic peptic ulcer with hemorrhage AND perforation	48
4280942	Acute gastrojejunal ulcer with perforation	34
4101870	Chronic gastrojejunal ulcer with perforation	21
4006994	Acute peptic ulcer with hemorrhage and perforation	20
4164920	Chronic gastrojejunal ulcer with hemorrhage AND perforation	12

Table 2.2.2 Included source concepts in DA-GERMANY for Ulcer

source_concept_code	source_concept_name	source_vocabulary_id	n
K25.9	Gastric ulcer, Unspecified as acute or chronic, without haemorrhage or perforation	ICD10	102227
K26.9	Duodenal ulcer, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	67248
K25.3	Gastric ulcer, Acute without haemorrhage or perforation	ICD10	13627
K27.9	Peptic ulcer, site unspecified, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	10968
K22.1	Ulcer of oesophagus	ICD10	9338
K26.3	Duodenal ulcer, acute without haemorrhage or perforation	ICD10	8099
K25.0	Gastric ulcer, Acute with haemorrhage	ICD10	5557
K25.7	Gastric ulcer, Chronic without haemorrhage or perforation	ICD10	5549
K25.4	Gastric ulcer, Chronic or unspecified with haemorrhage	ICD10	4028
K26.7	Duodenal ulcer, chronic without haemorrhage or perforation	ICD10	3565
K26.0	Duodenal ulcer, acute with haemorrhage	ICD10	2541
K25.5	Gastric ulcer, Chronic or unspecified with perforation	ICD10	2254
K28.9	Gastrojejunal ulcer, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	1951
K26.4	Duodenal ulcer, chronic or unspecified with haemorrhage	ICD10	1711
K25.1	Gastric ulcer, Acute with perforation	ICD10	636
K27.4	Peptic ulcer, site unspecified, chronic or unspecified with haemorrhage	ICD10	603
K25.2	Gastric ulcer, Acute with both haemorrhage and perforation	ICD10	490
K26.5	Duodenal ulcer, chronic or unspecified with perforation	ICD10	419
K27.7	Peptic ulcer, site unspecified, chronic without haemorrhage or perforation	ICD10	385

source_concept_code	source_concept_name	source_vocabulary_id	n
K27.5	Peptic ulcer, site unspecified, chronic or unspecified with perforation	ICD10	328
K27.3	Peptic ulcer, site unspecified, acute without haemorrhage or perforation	ICD10	326
K26.1	Duodenal ulcer, acute with perforation	ICD10	247
K28.7	Gastrojejunal ulcer, chronic without haemorrhage or perforation	ICD10	234
K26.2	Duodenal ulcer, acute with both haemorrhage and perforation	ICD10	216
K25.6	Gastric ulcer, Chronic or unspecified with both haemorrhage and perforation	ICD10	191
K27.0	Peptic ulcer, site unspecified, acute with haemorrhage	ICD10	167
K28.3	Gastrojejunal ulcer, acute without haemorrhage or perforation	ICD10	146
K27.1	Peptic ulcer, site unspecified, acute with perforation	ICD10	105
K26.6	Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation	ICD10	104
K28.4	Gastrojejunal ulcer, chronic or unspecified with haemorrhage	ICD10	85
K28.0	Gastrojejunal ulcer, acute with haemorrhage	ICD10	53
K28.2	Gastrojejunal ulcer, acute with both haemorrhage and perforation	ICD10	50
K27.6	Peptic ulcer, site unspecified, chronic or unspecified with both haemorrhage and perforation	ICD10	48
K28.1	Gastrojejunal ulcer, acute with perforation	ICD10	34
K28.5	Gastrojejunal ulcer, chronic or unspecified with perforation	ICD10	21
K27.2	Peptic ulcer, site unspecified, acute with both haemorrhage and perforation	ICD10	20
K28.6	Gastrojejunal ulcer, chronic or unspecified with both haemorrhage and perforation	ICD10	12

2.3. Chronic Renal Impairment

Table 2.3.1 Included standard concepts in DA-GERMANY for CRI

standard_concept_id	concept_name	n
192359	Renal failure syndrome	220052
46271022	Chronic kidney disease	136616
443597	Chronic kidney disease stage 3	73945
443601	Chronic kidney disease stage 2	57715
443614	Chronic kidney disease stage 1	18925
443612	Chronic kidney disease stage 4	17648
443611	Chronic kidney disease stage 5	16260
201313	Hypertensive renal disease	12182
193519	Impaired renal function disorder	8724
443919	Hypertensive renal failure	6835
195556	Hypertensive heart AND renal disease	4189
439696	Hypertensive heart and renal disease with (congestive) heart failure	3627
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	2790
439695	Hypertensive heart and renal disease with renal failure	1660
196455	Hepatorenal syndrome	837
37399017	Hemorrhagic fever with renal syndrome	633
4170452	Postoperative renal failure	431
4309006	Kidney transplant failure and rejection	334
4149398	Congenital renal failure	176
4057978	Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium	15
45757356	Pre-existing hypertensive chronic kidney disease in mother complicating pregnancy	15

Table 2.3.2 Included source concepts in DA-GERMANY for CRI

source_concept_code	source_concept_name	source_vocabulary_id	n
N19	Unspecified kidney failure	ICD10	220052
N18.9	Chronic kidney disease, unspecified	ICD10	136616
N18.3	Chronic kidney disease, stage 3	ICD10	73945
N18.2	Chronic kidney disease, stage 2	ICD10	57715
N18.1	Chronic kidney disease, stage 1	ICD10	18925
N18.4	Chronic kidney disease, stage 4	ICD10	17648
N18.5	Chronic kidney disease, stage 5	ICD10	16260
I12.9	Hypertensive renal disease without renal failure	ICD10	12182
I12.0	Hypertensive renal disease with renal failure	ICD10	6835
N25.9	Disorder resulting from impaired renal tubular function, unspecified	ICD10	5916
I13.9	Hypertensive heart and renal disease, unspecified	ICD10	4189
I13.0	Hypertensive heart and renal disease with (congestive) heart failure	ICD10	3627
N25.8	Other disorders resulting from impaired renal tubular function	ICD10	2808
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	ICD10	2790

source_concept_code	source_concept_name	source_vocabulary_id	n
I13.1	Hypertensive heart and renal disease with renal failure	ICD10	1660
K76.7	Hepatorenal syndrome	ICD10	837
A98.5	Haemorrhagic fever with renal syndrome	ICD10	633
N99.0	Postprocedural renal failure	ICD10	431
T86.1	Kidney transplant failure and rejection	ICD10	334
P96.0	Congenital renal failure	ICD10	176
O10.2	Pre-existing hypertensive renal disease complicating pregnancy, childbirth and the puerperium	ICD10	15
O10.3	Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium	ICD10	15

3. IMRD

3.1. GERD

Table 3.1.1 Included standard concepts in IMRD for GERD

standard_concept_id	concept_name	n
30437	Gastro-esophageal reflux disease with esophagitis	191024
318800	Gastroesophageal reflux disease	182395
44783954	Acid reflux	110684
4144111	Gastroesophageal reflux disease without esophagitis	2653
4046097	Sandifer syndrome	44

Table 3.1.2 Included source concepts in IMRD for GERD

source_concept_code	source_concept_name	source_vocabulary_id	n
J10y412	Gastro-oesophageal reflux	Read	182395
J101100	Reflux oesophagitis	Read	172690
J10y413	Acid reflux	Read	101463
J101112	Gastro-oesophageal reflux with oesophagitis	Read	13495
J101111	Acid reflux	Read	9221
J101113	Oesophageal reflux with oesophagitis	Read	4331
J10y400	Oesopheal reflux without mention of oesophagitis	Read	2653
J101115	Regurgitant oesophagitis	Read	318
J101114	Peptic oesophagitis	Read	190
J34y.11	Sandifer's syndrome	Read	44

3.2. Zollinger Ellison Syndrome

Table 3.2.1 Included standard concepts in IMRD for ZES

standard_concept_id	concept_name	n
4200399	Zollinger-Ellison syndrome	52

Table 3.2.2 Included source concepts in IMRD for ZES

source_concept_code	source_concept_name	source_vocabulary_id	n
C115.11	Zollinger - Ellison syndrome	Read	52
C115000	Excessive gastrin secretion	Read	0

3.3. Gastric Or Duodenal Ulcer

Table 3.3.1 Included standard concepts in IMRD for Ulcer

standard_concept_id	concept_name	n
4198381	Ulcer of duodenum	22642
4265600	Gastric ulcer	18801
4027663	Peptic ulcer	3763
4341235	Multiple gastric erosions	3680
25844	Ulcer of esophagus	3382
4025500	Barrett's ulcer of esophagus	1627
4173408	Chronic duodenal ulcer with perforation	865
4189591	Pyloric ulcer	856
4206524	Ulcerative esophagitis	757
4340230	Duodenal erosion	615
4331322	Prepyloric ulcer	393
4231580	Acute gastric ulcer with hemorrhage	373
4059178	Gastrojejunal ulcer	355
4232181	Chronic duodenal ulcer with hemorrhage	293
4229614	Duodenal ulcer with perforation	272
4150681	Chronic gastric ulcer with perforation	224
4028242	Chronic duodenal ulcer	217
4318534	Chronic gastric ulcer	186
4057053	Acute duodenal ulcer	170
4265479	Acute duodenal ulcer with perforation	163
4057076	Healed gastric ulcer leaving a scar	156
4027729	Acute duodenal ulcer with hemorrhage	147
4319441	Acute gastric ulcer	144
4197598	Multiple gastric ulcers	117
4057060	Acute peptic ulcer	55
4200399	Zollinger-Ellison syndrome	52
44791257	Non-steroidal anti-inflammatory drug induced gastric ulcer	51
4211001	Chronic gastric ulcer with hemorrhage	50
4099014	Duodenal ulcer with hemorrhage	43
4057953	Acute gastric ulcer with perforation	38
4229422	Fungal ulcer of esophagus	27
4194543	Acute peptic ulcer with perforation	23
4024842	Recurrent duodenal ulcer	19
36716253	Duodenal ulcer caused by non-steroidal anti-inflammatory drug	14
4024831	Esophageal ulcer due to aspirin	13
4134146	Chronic peptic ulcer	13
4273255	Ulcer of esophagus due to ingestion of medicines	12
4046500	Acute peptic ulcer with hemorrhage	10
4049466	Gastric ulcer with hemorrhage	10
4321586	Gastric ulcer with perforation	10
4024984	Acute gastrojejunal ulcer	7
4080599	Gastrocolic ulcer	7
436453	Chronic duodenal ulcer with obstruction	0
4024840	Acute duodenal ulcer with obstruction	0
4028243	Chronic gastrojejunal ulcer	0
4055895	Chronic gastric ulcer with obstruction	0
4146517	Chronic peptic ulcer with perforation	0
4169592	Acute gastric ulcer with hemorrhage AND perforation	0
4174044	Chronic peptic ulcer with hemorrhage	0

standard_concept_id	concept_name	n
4174560	Duodenal ulcer induced by anti-platelet agent	0
4217947	Acute gastrojejunal ulcer with hemorrhage AND perforation	0
4267306	Ulcer of esophagus due to ingestion of chemical	0
4274491	Acute gastrojejunal ulcer with hemorrhage	0
4280942	Acute gastrojejunal ulcer with perforation	0
4289830	Chronic duodenal ulcer with hemorrhage AND perforation	0
4294973	Chronic gastric ulcer with hemorrhage AND with perforation	0
4310838	Gastric ulcer induced by anti-platelet agent	0
4336230	Acute duodenal ulcer with hemorrhage AND perforation	0
44808500	Duodenal ulcer with obstruction	0

Table 3.3.2 Included source concepts in IMRD for Ulcer

source_concept_code	source_concept_name	source_vocabulary_id	n
J12..00	Duodenal ulcer - (DU)	Read	22016
J11..00	Gastric ulcer - (GU)	Read	18351
J11z.11	Gastric erosions	Read	3680
J13..00	Peptic ulcer - (PU) site unspecified	Read	3267
J102.00	Ulcer of oesophagus	Read	3245
J102500	Barrett's ulcer of oesophagus	Read	1627
J11..12	Pyloric ulcer	Read	856
J121211	Perforated chronic duodenal ulcer	Read	820
J101600	Ulcerative oesophagitis	Read	757
J123.00	Duodenal erosion	Read	615
J12z.00	Duodenal ulcer NOS	Read	560
J11z.00	Gastric ulcer NOS	Read	421
J11..11	Prepyloric ulcer	Read	393
J13z.00	Peptic ulcer NOS	Read	382
J110111	Bleeding acute gastric ulcer	Read	313
J12y200	Unspecified duodenal ulcer with perforation	Read	272
J121111	Bleeding chronic duodenal ulcer	Read	267
J111211	Perforated chronic gastric ulcer	Read	209
J121.00	Chronic duodenal ulcer	Read	197
J14..15	Stomal ulcer	Read	195
J120200	Acute duodenal ulcer with perforation	Read	163
J111.00	Chronic gastric ulcer	Read	157
J17y800	Healed gastric ulcer leaving a scar	Read	156
J120.00	Acute duodenal ulcer	Read	148
J120100	Acute duodenal ulcer with haemorrhage	Read	147
J102z00	Ulcer of oesophagus NOS	Read	137
J110.00	Acute gastric ulcer	Read	126
J11z.12	Multiple gastric ulcers	Read	117
J14..14	Marginal ulcer	Read	85
J13..11	Stress ulcer NOS	Read	69
J110100	Acute gastric ulcer with haemorrhage	Read	60
J130.00	Acute peptic ulcer	Read	55
C115.11	Zollinger - Ellison syndrome	Read	52
J113.00	Non steroidal anti inflammatory drug induced gastric ulcer	Read	51
J121200	Chronic duodenal ulcer with perforation	Read	45

source_concept_code	source_concept_name	source_vocabulary_id	n
J12y100	Unspecified duodenal ulcer with haemorrhage	Read	43
J14..11	Anastomotic ulcer	Read	41
J122.00	Duodenal ulcer disease	Read	40
J110200	Acute gastric ulcer with perforation	Read	38
J111111	Bleeding chronic gastric ulcer	Read	34
J102100	Fungal ulcer of oesophagus	Read	27
J14..00	Gastrojejunal ulcer (GJU)	Read	27
J121100	Chronic duodenal ulcer with haemorrhage	Read	26
J13y.00	Unspecified peptic ulcer	Read	24
J130200	Acute peptic ulcer with perforation	Read	23
J11y.00	Unspecified gastric ulcer	Read	22
J12y.00	Unspecified duodenal ulcer	Read	20
J124.00	Recurrent duodenal ulcer	Read	19
J111z00	Chronic gastric ulcer NOS	Read	18
J111100	Chronic gastric ulcer with haemorrhage	Read	16
J111200	Chronic gastric ulcer with perforation	Read	15
J126.00	Non steroidal anti inflammatory drug induced duodenal ulcer	Read	14
J102200	Oesophageal ulcer due to aspirin	Read	13
J131.00	Chronic peptic ulcer	Read	13
J102400	Oesophageal ulcer due to medicines	Read	12
J110000	Acute gastric ulcer without mention of complication	Read	12
J121z00	Chronic duodenal ulcer NOS	Read	12
J111000	Chronic gastric ulcer without mention of complication	Read	11
J120000	Acute duodenal ulcer without mention of complication	Read	11
J120z00	Acute duodenal ulcer NOS	Read	11
J11y100	Unspecified gastric ulcer with haemorrhage	Read	10
J11y200	Unspecified gastric ulcer with perforation	Read	10
J130100	Acute peptic ulcer with haemorrhage	Read	10
J121000	Chronic duodenal ulcer without mention of complication	Read	8
J13y200	Unspecified peptic ulcer with perforation	Read	8
J13yz00	Unspecified peptic ulcer NOS	Read	8
J11yz00	Unspecified gastric ulcer NOS	Read	7
J14..12	Gastrocolic ulcer	Read	7
J140.00	Acute gastrojejunal ulcer	Read	7
J14z.00	Gastrojejunal ulcer NOS	Read	7
J110z00	Acute gastric ulcer NOS	Read	6
J12yz00	Unspecified duodenal ulcer NOS	Read	6
J13y100	Unspecified peptic ulcer with haemorrhage	Read	5
C115000	Excessive gastrin secretion	Read	0
J102300	Oesophageal ulcer due to chemicals	Read	0

source_concept_code	source_concept_name	source_vocabulary_id	n
J110300	Acute gastric ulcer with haemorrhage and perforation	Read	0
J110y00	Acute gastric ulcer unspecified	Read	0
J111300	Chronic gastric ulcer with haemorrhage and perforation	Read	0
J111400	Chronic gastric ulcer with obstruction	Read	0
J111y00	Chronic gastric ulcer unspecified	Read	0
J112.00	Anti-platelet induced gastric ulcer	Read	0
J112z00	Anti-platelet induced gastric ulcer NOS	Read	0
J113z00	Non steroidal anti inflammatory drug induced gastric ulcer NOS	Read	0
J11y000	Unspecified gastric ulcer without mention of complication	Read	0
J120300	Acute duodenal ulcer with haemorrhage and perforation	Read	0
J120400	Acute duodenal ulcer with obstruction	Read	0
J120y00	Acute duodenal ulcer unspecified	Read	0
J121300	Chronic duodenal ulcer with haemorrhage and perforation	Read	0
J121400	Chronic duodenal ulcer with obstruction	Read	0
J121y00	Chronic duodenal ulcer unspecified	Read	0
J125.00	Anti-platelet induced duodenal ulcer	Read	0
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation	Read	0
J12y400	Unspecified duodenal ulcer with obstruction	Read	0
J12yy00	Unspecified duodenal ulcer with unspecified haemorrhage and/or perforation	Read	0
J130y00	Acute peptic ulcer unspecified	Read	0
J130z00	Acute peptic ulcer NOS	Read	0
J131100	Chronic peptic ulcer with haemorrhage	Read	0
J131200	Chronic peptic ulcer with perforation	Read	0
J131z00	Chronic peptic ulcer NOS	Read	0
J13y000	Unspecified peptic ulcer without mention of complication	Read	0
J140100	Acute gastrojejunal ulcer with haemorrhage	Read	0
J140200	Acute gastrojejunal ulcer with perforation	Read	0
J140300	Acute gastrojejunal ulcer with haemorrhage and perforation	Read	0
J140z00	Acute gastrojejunal ulcer NOS	Read	0
J141y00	Chronic gastrojejunal ulcer unspecified	Read	0
J14y.00	Unspecified gastrojejunal ulcer	Read	0
J14yz00	Unspecified gastrojejunal ulcer NOS	Read	0

3.4. Chronic Renal Impairment

Table 3.4.1 Included standard concepts in IMRD for CRI

standard_concept_id	concept_name	n
443597	Chronic kidney disease stage 3	329496
443601	Chronic kidney disease stage 2	67727
443612	Chronic kidney disease stage 4	33961
198185	Chronic renal failure	26699
45763854	Chronic kidney disease stage 3A	20157
46271022	Chronic kidney disease	14335
443614	Chronic kidney disease stage 1	13598
4030518	Renal impairment	13495
44792249	CKD stage 3A without proteinuria	10278
192359	Renal failure syndrome	9729
44792231	CKD stage 3 without proteinuria	8935
45763855	Chronic kidney disease stage 3B	7392
443611	Chronic kidney disease stage 5	7352
193519	Impaired renal function disorder	3864
44792251	CKD stage 3B without proteinuria	3754
44792230	CKD stage 3 with proteinuria	2787
193782	End-stage renal disease	2724
44792232	CKD stage 3A with proteinuria	1725
44792229	CKD stage 2 without proteinuria	1673
46287169	CKD G2A2 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A2	1419
44792253	CKD stage 4 without proteinuria	1319
44792250	CKD stage 3B with proteinuria	1249
44792252	CKD stage 4 with proteinuria	1178
46284587	CKD G3aA1 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A1	1093
201313	Hypertensive renal disease	848
4150547	Anemia secondary to renal failure	636
46286992	CKD G3aA2 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A2	624
44792228	CKD stage 2 with proteinuria	479
443961	Anemia of chronic renal failure	454
46284591	CKD G3bA1 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A1	448
46284592	CKD G3bA2 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A2	417
44792254	CKD stage 5 with proteinuria	359
196455	Hepatorenal syndrome	252
44792255	CKD stage 5 without proteinuria	142
44792227	CKD stage 1 without proteinuria	138
46284572	CKD G2A1 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A1	136
4128067	Acute-on-chronic renal failure	114
4309006	Kidney transplant failure and rejection	114
4153876	Renal failure as a complication of care	97
46284597	CKD G4A1 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A1	94
46284588	CKD G3aA3 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A3	90
44792226	CKD stage 1 with proteinuria	88
46284593	CKD G3bA3 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A3	83
4170452	Postoperative renal failure	68

standard_concept_id	concept_name	n
46284598	CKD G4A2 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A2	66
46284599	CKD G4A3 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A3	52
439695	Hypertensive heart and renal disease with renal failure	31
46284600	CKD G5A1 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A1	22
442766	Malignant hypertensive renal disease	21
46284603	CKD G5A3 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A3	21
439696	Hypertensive heart and renal disease with (congestive) heart failure	20
46284575	CKD G2A3 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A3	17
193493	Benign hypertensive renal disease	14
46284567	CKD G1A2 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A2	14
46284566	CKD G1A1 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A1	11
4149398	Congenital renal failure	9
46284570	CKD G1A3 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A3	8
46284602	CKD G5A2 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A2	8
195556	Hypertensive heart AND renal disease	7
4056470	Renal function impairment with growth failure	5
197930	Renal hypertension complicating pregnancy, childbirth and the puerperium	0
200157	Renal hypertension complicating pregnancy, childbirth and the puerperium - delivered	0
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	0
4054914	Phosphate-losing tubular disorders	0
4057978	Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium	0
4341540	Renal acidemia	0
43530912	Induced termination of pregnancy complicated by renal failure	0

Table 3.4.2 Included source concepts in IMRD for CRI

source_concept_code	source_concept_name	source_vocabulary_id	n
1Z12.00	Chronic kidney disease stage 3	Read	312280
1Z11.00	Chronic kidney disease stage 2	Read	67308
1Z13.00	Chronic kidney disease stage 4	Read	32514
K05..00	Chronic renal failure	Read	26557
1Z15.00	Chronic kidney disease stage 3A	Read	20157
K053.00	Chronic kidney disease stage 3	Read	17216
1Z1..00	Chronic renal impairment	Read	14065
1Z10.00	Chronic kidney disease stage 1	Read	13521
K060.00	Renal impairment	Read	10369
1Z1E.00	Chronic kidney disease stage 3A without proteinuria	Read	10198
K06..00	Renal failure unspecified	Read	9626

source_concept_code	source_concept_name	source_vocabulary_id	n
1Z1C.00	Chronic kidney disease stage 3 without proteinuria	Read	8823
1Z16.00	Chronic kidney disease stage 3B	Read	7392
1Z14.00	Chronic kidney disease stage 5	Read	6963
1Z1G.00	Chronic kidney disease stage 3B without proteinuria	Read	3719
K08..00	Impaired renal function disorder	Read	3262
K060.11	Impaired renal function	Read	3126
1Z1B.00	Chronic kidney disease stage 3 with proteinuria	Read	2731
K050.00	End stage renal failure	Read	2282
1Z1D.00	Chronic kidney disease stage 3A with proteinuria	Read	1703
1Z1A.00	Chronic kidney disease stage 2 without proteinuria	Read	1654
K054.00	Chronic kidney disease stage 4	Read	1447
1Z1R.00	CKD G2A2 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A2	Read	1419
1Z1J.00	Chronic kidney disease stage 4 without proteinuria	Read	1254
1Z1F.00	Chronic kidney disease stage 3B with proteinuria	Read	1225
1Z1H.00	Chronic kidney disease stage 4 with proteinuria	Read	1114
1Z1T.00	CKD G3aA1 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A1	Read	1093
D215.00	Anaemia secondary to renal failure	Read	636
1Z1V.00	CKD G3aA2 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A2	Read	624
K08z.00	Impaired renal function disorder NOS	Read	555
G22..00	Hypertensive renal disease	Read	479
1Z19.00	Chronic kidney disease stage 2 with proteinuria	Read	469
D215000	Anaemia secondary to chronic renal failure	Read	454
1Z1X.00	CKD G3bA1 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A1	Read	448
K052.00	Chronic kidney disease stage 2	Read	419
1Z1Y.00	CKD G3bA2 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A2	Read	417
K055.00	Chronic kidney disease stage 5	Read	389
K0D..00	End-stage renal disease	Read	323

source_concept_code	source_concept_name	source_vocabulary_id	n
1Z1K.00	Chronic kidney disease stage 5 with proteinuria	Read	319
K05..13	Chronic kidney disease	Read	270
J624.00	Hepatorenal syndrome	Read	252
G22..11	Nephrosclerosis	Read	241
K05..11	Chronic uraemia	Read	137
1Z1Q.00	CKD G2A1 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A1	Read	136
1Z18.00	Chronic kidney disease stage 1 without proteinuria	Read	133
1Z1L.00	Chronic kidney disease stage 5 without proteinuria	Read	120
K05..12	End stage renal failure	Read	119
K0E..00	Acute-on-chronic renal failure	Read	114
SP08300	Kidney transplant failure and rejection	Read	114
1Z1C.11	CKD stage 3 without proteinuria	Read	112
1Z1a.00	CKD G4A1 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A1	Read	94
1Z1W.00	CKD G3aA3 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A3	Read	90
1Z17.00	Chronic kidney disease stage 1 with proteinuria	Read	83
1Z1Z.00	CKD G3bA3 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A3	Read	83
Kyu2.00	[X]Renal failure	Read	81
1Z1E.11	CKD stage 3A without proteinuria	Read	80
K051.00	Chronic kidney disease stage 1	Read	77
SP15412	Post operative renal failure	Read	68
1Z1b.00	CKD G4A2 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A2	Read	66
1Z1J.11	CKD stage 4 without proteinuria	Read	65
G22z.11	Renal hypertension	Read	65
1Z1H.11	CKD stage 4 with proteinuria	Read	64
G22z.00	Hypertensive renal disease NOS	Read	63
1Z1B.11	CKD stage 3 with proteinuria	Read	56
1Z1c.00	CKD G4A3 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A3	Read	52
SP15400	Renal failure as a complication of care	Read	51

source_concept_code	source_concept_name	source_vocabulary_id	n
SP15411	Kidney failure as a complication of care	Read	46
1Z1K.11	CKD stage 5 with proteinuria	Read	40
1Z1G.11	CKD stage 3B without proteinuria	Read	35
K08yz00	Other impaired renal function disorder NOS	Read	32
G233.00	Hypertensive heart and renal disease with renal failure	Read	31
1Z1F.11	CKD stage 3B with proteinuria	Read	24
1Z1d.00	CKD G5A1 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A1	Read	22
1Z1D.11	CKD stage 3A with proteinuria	Read	22
1Z1L.11	CKD stage 5 without proteinuria	Read	22
K06..12	Kidney failure unspecified	Read	22
1Z1f.00	CKD G5A3 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A3	Read	21
G220.00	Malignant hypertensive renal disease	Read	21
G232.00	Hypertensive heart and renal disease with (congestive) heart failure	Read	20
1Z1A.11	CKD stage 2 without proteinuria	Read	19
1Z1S.00	CKD G2A3 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A3	Read	17
K08y.00	Other impaired renal function disorder	Read	15
1Z1N.00	CKD G1A2 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A2	Read	14
G221.00	Benign hypertensive renal disease	Read	14
1Z1M.00	CKD G1A1 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A1	Read	11
1Z19.11	CKD stage 2 with proteinuria	Read	10
Q48y000	Congenital renal failure	Read	9
1Z1e.00	CKD G5A2 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A2	Read	8
1Z1P.00	CKD G1A3 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A3	Read	8
G23..00	Hypertensive heart and renal disease	Read	7
1Z17.11	CKD stage 1 with proteinuria	Read	5
1Z18.11	CKD stage 1 without proteinuria	Read	5

source_concept_code	source_concept_name	source_vocabulary_id	n
K08y300	Renal function impairment with growth failure	Read	5
Kyu2100	[X]Other chronic renal failure	Read	5
G234.00	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	Read	0
G23z.00	Hypertensive heart and renal disease NOS	Read	0
K080000	Phosphate-losing tubular disorders	Read	0
K08yz11	Renal acidaemia	Read	0
L093.00	Renal failure following abortive pregnancy	Read	0
L121.00	Renal hypertension complicating pregnancy, childbirth and the puerperium	Read	0
L121100	Renal hypertension complicating pregnancy, childbirth and the puerperium - delivered	Read	0
L128100	Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium	Read	0
SP15413	Uraemia - post operative	Read	0

4. IPCI

4.1. GERD

Table 4.1.1 Included standard concepts in IPCI for GERD

standard_concept_id	concept_name	n
4144111	Gastroesophageal reflux disease without esophagitis	24482
30437	Gastro-esophageal reflux disease with esophagitis	15753

Table 4.1.2 Included source concepts in IPCI for GERD

source_concept_code	source_concept_name	source_vocabulary_id	n
D84.02	Oesophageal reflux disease without oesophagitis	ICPC-1	24482
D84.03	Oesophageal reflux with oesophagitis	ICPC-1	15753

4.2. Gastric Or Duodenal Ulcer

Table 4.2.1 Included standard concepts in IPCI for Ulcer

standard_concept_id	concept_name	n
4027663	Peptic ulcer	3984
4198381	Duodenal ulcer disease	3005
4265600	Gastric ulcer	1642

Table 4.2.2 Included source concepts in IPCI for Ulcer

source_concept_code	source_concept_name	source_vocabulary_id	n
D86.00	Peptic ulcer other	ICPC-1	3984
D85.00	Duodenal ulcer	ICPC-1	3005
D86.01	Gastric ulcer	ICPC-1	1642

4.3. Chronic Renal Impairment

Table 4.3.1 Included standard concepts in IPCI for CRI

standard_concept_id	concept_name	n
192359	Renal failure syndrome	46209

Table 4.3.2 Included source concepts in IPCI for CRI

source_concept_code	source_concept_name	source_vocabulary_id	n
U99.01	Renal insufficiency	ICPC-1	46209

5. LPD-BELGIUM

5.1. GERD

Table 5.1.1 Included standard concepts in LPD-BELGIUM for GERD

standard_concept_id	concept_name	n
318800	Gastroesophageal reflux disease	85882
30437	Gastro-esophageal reflux disease with esophagitis	14470
4144111	Gastroesophageal reflux disease without esophagitis	4665

Table 5.1.2 Included source concepts in LPD-BELGIUM for GERD

source_concept_code	source_concept_name	source_vocabulary_id	n
K21	Gastro-oesophageal reflux disease	ICD10	85882
K21.0	Gastro-oesophageal reflux disease with oesophagitis	ICD10	14470
K21.9	Gastro-oesophageal reflux disease without oesophagitis	ICD10	4665

5.2. Gastric Or Duodenal Ulcer

Table 5.2.1 Included standard concepts in LPD-BELGIUM for Ulcer

standard_concept_id	concept_name	n
4027663	Peptic ulcer	9091
4265600	Gastric ulcer	1043
4291028	Peptic ulcer without hemorrhage AND without perforation	876
4198381	Ulcer of duodenum	811
25844	Ulcer of esophagus	154

Table 5.2.2 Included source concepts in LPD-BELGIUM for Ulcer

source_concept_code	source_concept_name	source_vocabulary_id	n
K27	Peptic ulcer, site unspecified	ICD10	9091
K25	Gastric ulcer	ICD10	1043
K27.9	Peptic ulcer, site unspecified, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	876
K26	Duodenal ulcer	ICD10	811
K22.1	Ulcer of oesophagus	ICD10	154

5.3. Chronic Renal Impairment

Table 5.3.1 Included standard concepts in LPD-BELGIUM for CRI

standard_concept_id	concept_name	n
46271022	Chronic kidney disease	5842
192359	Renal failure syndrome	229
193782	End-stage renal disease	125
193519	Impaired renal function disorder	94
443919	Hypertensive renal failure	7

Table 5.3.2 Included source concepts in LPD-BELGIUM for CRI

source_concept_code	source_concept_name	source_vocabulary_id	n
N18	Chronic kidney disease	ICD10	5842
N19	Unspecified kidney failure	ICD10	229
N18.0	End-stage renal disease	ICD10	125
N25.8	Other disorders resulting from impaired renal tubular function	ICD10	94

source_concept_code	source_concept_name	source_vocabulary_id	n
I12.0	Hypertensive renal disease with renal failure	ICD10	7

6. SIDIAP

6.1. GERD

Table 6.1.1 Included standard concepts in SIDIAP for GERD

standard_concept_id	concept_name	n
4144111	Gastroesophageal reflux disease without esophagitis	211603
318800	Gastroesophageal reflux disease	29028
30437	Gastro-esophageal reflux disease with esophagitis	2359

Table 6.1.2 Included source concepts in SIDIAP for GERD

source_concept_code	source_concept_name	source_vocabulary_id	n
K21.9	Gastro-oesophageal reflux disease without oesophagitis	ICD10	211603
K21	Gastro-oesophageal reflux disease	ICD10	29028
K21.0	Gastro-oesophageal reflux disease with oesophagitis	ICD10	2359

6.2. Gastric Or Duodenal Ulcer

Table 6.2.1 Included standard concepts in SIDIAP for Ulcer

standard_concept_id	concept_name	n
4198381	Ulcer of duodenum	15255
4265600	Gastric ulcer	9783
4248429	Gastric ulcer without hemorrhage AND without perforation	8100
4027663	Peptic ulcer	6870
4209746	Duodenal ulcer without hemorrhage AND without perforation	6720
4173408	Chronic duodenal ulcer with perforation	1753
4291028	Peptic ulcer without hemorrhage AND without perforation	1360
4150681	Chronic gastric ulcer with perforation	1216
25844	Ulcer of esophagus	783
4231580	Acute gastric ulcer with hemorrhage	713
4195231	Acute gastric ulcer without hemorrhage AND without perforation	680
4027729	Acute duodenal ulcer with hemorrhage	667
4146517	Chronic peptic ulcer with perforation	472
4057953	Acute gastric ulcer with perforation	215
4265479	Acute duodenal ulcer with perforation	134
4138962	Acute duodenal ulcer without hemorrhage AND without perforation	97
4046500	Acute peptic ulcer with hemorrhage	80
4222896	Chronic duodenal ulcer without hemorrhage AND without perforation	74
4211001	Chronic gastric ulcer with hemorrhage	59
4232181	Chronic duodenal ulcer with hemorrhage	55
4169592	Acute gastric ulcer with hemorrhage AND perforation	52
4296611	Chronic gastric ulcer without hemorrhage AND without perforation	46
4101104	Gastrojejunal ulcer without hemorrhage AND without perforation	43
4059178	Gastrojejunal ulcer	37
4336230	Acute duodenal ulcer with hemorrhage AND perforation	37
4274491	Acute gastrojejunal ulcer with hemorrhage	19
4289830	Chronic duodenal ulcer with hemorrhage AND perforation	17
4174044	Chronic peptic ulcer with hemorrhage	16

standard_concept_id	concept_name	n
4294973	Chronic gastric ulcer with hemorrhage AND with perforation	14
4163865	Acute peptic ulcer without hemorrhage AND without perforation	10
433515	Chronic gastrojejunal ulcer with hemorrhage	9
4194543	Acute peptic ulcer with perforation	8
4204555	Chronic peptic ulcer without hemorrhage AND without perforation	8
4247008	Chronic peptic ulcer with hemorrhage AND perforation	7
4280942	Acute gastrojejunal ulcer with perforation	7
4006994	Acute peptic ulcer with hemorrhage and perforation	5
4101870	Chronic gastrojejunal ulcer with perforation	0
4147683	Acute gastrojejunal ulcer without hemorrhage AND without perforation	0
4164920	Chronic gastrojejunal ulcer with hemorrhage AND perforation	0
4177387	Chronic gastrojejunal ulcer without hemorrhage AND without perforation	0

Table 6.2.2 Included source concepts in SIDIAP for Ulcer

source_concept_code	source_concept_name	source_vocabulary_id	n
K26	Duodenal ulcer	ICD10	15255
K25	Gastric ulcer	ICD10	9783
K25.9	Gastric ulcer, Unspecified as acute or chronic, without haemorrhage or perforation	ICD10	8100
K27	Peptic ulcer, site unspecified	ICD10	6870
K26.9	Duodenal ulcer, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	6720
K26.5	Duodenal ulcer, chronic or unspecified with perforation	ICD10	1753
K27.9	Peptic ulcer, site unspecified, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	1360
K25.5	Gastric ulcer, Chronic or unspecified with perforation	ICD10	1216
K22.1	Ulcer of oesophagus	ICD10	783
K25.0	Gastric ulcer, Acute with haemorrhage	ICD10	713
K25.3	Gastric ulcer, Acute without haemorrhage or perforation	ICD10	680
K26.0	Duodenal ulcer, acute with haemorrhage	ICD10	667
K27.5	Peptic ulcer, site unspecified, chronic or unspecified with perforation	ICD10	472
K25.1	Gastric ulcer, Acute with perforation	ICD10	215
K26.1	Duodenal ulcer, acute with perforation	ICD10	134
K26.3	Duodenal ulcer, acute without haemorrhage or perforation	ICD10	97
K27.0	Peptic ulcer, site unspecified, acute with haemorrhage	ICD10	80
K26.7	Duodenal ulcer, chronic without haemorrhage or perforation	ICD10	74
K25.4	Gastric ulcer, Chronic or unspecified with haemorrhage	ICD10	59

source_concept_code	source_concept_name	source_vocabulary_id	n
K26.4	Duodenal ulcer, chronic or unspecified with haemorrhage	ICD10	55
K25.2	Gastric ulcer, Acute with both haemorrhage and perforation	ICD10	52
K25.7	Gastric ulcer, Chronic without haemorrhage or perforation	ICD10	46
K28.9	Gastrojejunal ulcer, unspecified as acute or chronic, without haemorrhage or perforation	ICD10	43
K26.2	Duodenal ulcer, acute with both haemorrhage and perforation	ICD10	37
K28	Gastrojejunal ulcer	ICD10	37
K28.0	Gastrojejunal ulcer, acute with haemorrhage	ICD10	19
K26.6	Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation	ICD10	17
K27.4	Peptic ulcer, site unspecified, chronic or unspecified with haemorrhage	ICD10	16
K25.6	Gastric ulcer, Chronic or unspecified with both haemorrhage and perforation	ICD10	14
K27.3	Peptic ulcer, site unspecified, acute without haemorrhage or perforation	ICD10	10
K28.4	Gastrojejunal ulcer, chronic or unspecified with haemorrhage	ICD10	9
K27.1	Peptic ulcer, site unspecified, acute with perforation	ICD10	8
K27.7	Peptic ulcer, site unspecified, chronic without haemorrhage or perforation	ICD10	8
K27.6	Peptic ulcer, site unspecified, chronic or unspecified with both haemorrhage and perforation	ICD10	7
K28.1	Gastrojejunal ulcer, acute with perforation	ICD10	7
K27.2	Peptic ulcer, site unspecified, acute with both haemorrhage and perforation	ICD10	5
K28.3	Gastrojejunal ulcer, acute without haemorrhage or perforation	ICD10	0
K28.5	Gastrojejunal ulcer, chronic or unspecified with perforation	ICD10	0
K28.6	Gastrojejunal ulcer, chronic or unspecified with both haemorrhage and perforation	ICD10	0
K28.7	Gastrojejunal ulcer, chronic without haemorrhage or perforation	ICD10	0

6.3. Chronic Renal Impairment

Table 6.3.1 Included standard concepts in SIDIAP for CRI

standard_concept_id	concept_name	n
46271022	Chronic kidney disease	287630
192359	Renal failure syndrome	2700
201313	Hypertensive renal disease	2366
198185	Chronic renal failure	532
193519	Impaired renal function disorder	375
195556	Hypertensive heart AND renal disease	336
443919	Hypertensive renal failure	222
193782	End-stage renal disease	174
439695	Hypertensive heart and renal disease with renal failure	70
4309006	Kidney transplant failure and rejection	39
4170452	Postoperative renal failure	35
196455	Hepatorenal syndrome	31
439696	Hypertensive heart and renal disease with (congestive) heart failure	30
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	20
4149398	Congenital renal failure	6
4057978	Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium	0
37399017	Hemorrhagic fever with renal syndrome	0
45757356	Pre-existing hypertensive chronic kidney disease in mother complicating pregnancy	0

Table 6.3.2 Included source concepts in SIDIAP for CRI

source_concept_code	source_concept_name	source_vocabulary_id	n
N18.9	Chronic kidney disease, unspecified	ICD10	252157
N18	Chronic kidney disease	ICD10	35473
N19	Unspecified kidney failure	ICD10	2700
I12.9	Hypertensive renal disease without renal failure	ICD10	1521
I12	Hypertensive renal disease	ICD10	845
N18.8	Other chronic renal failure	ICD10	532
I13	Hypertensive heart and renal disease	ICD10	309
I12.0	Hypertensive renal disease with renal failure	ICD10	222
N18.0	End-stage renal disease	ICD10	174
N25	Disorders resulting from impaired renal tubular function	ICD10	167
N25.9	Disorder resulting from impaired renal tubular function, unspecified	ICD10	116
N25.8	Other disorders resulting from impaired renal tubular function	ICD10	92
I13.1	Hypertensive heart and renal disease with renal failure	ICD10	70
T86.1	Kidney transplant failure and rejection	ICD10	39
N99.0	Postprocedural renal failure	ICD10	35
K76.7	Hepatorenal syndrome	ICD10	31
I13.0	Hypertensive heart and renal disease with (congestive) heart failure	ICD10	30

source_concept_code	source_concept_name	source_vocabulary_id	n
I13.9	Hypertensive heart and renal disease, unspecified	ICD10	27
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	ICD10	20
P96.0	Congenital renal failure	ICD10	6
A98.5	Haemorrhagic fever with renal syndrome	ICD10	0
O10.2	Pre-existing hypertensive renal disease complicating pregnancy, childbirth and the puerperium	ICD10	0
O10.3	Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium	ICD10	0

Annex 5. DDD of H_2-receptor antagonist ingredients

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