Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

Drug usage patterns of Pylera® in France using the national claims reimbursement database

Study Protocol V6.0
11 February 2016

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PROTOCOL/AMENDMENT APPROVAL PAGE

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PASS INFORMATION

Title	DUS: Drug Usage patternS of Pylera® in France using the national claims reimbursement database
Protocol version	V6.0
Date of last version of protocol	11 February 2016
EU PASS register number	ENCEPP/SDPP/3901
Active substance	Bismuth subcitrate potassium, metronidazole, tetracycline hydrochloride (A02BD08)
Medicinal product	Pylera
Product reference	CIP: 2180420
Procedure number	DE/H/2467/001/DC
Marketing authorisation holder	Aptalis Pharma
Joint PASS	No
Research question and objectives	The objective of the study is to describe the usage patterns of Pylera® in real-life practice.
Country of study	France
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This study was conducted in accordance with Good Pharmacoepidemiology Practices.

This study is an "ENCePP Seal Study" and was conducted in accordance with the ENCePP Code of Conduct.

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2 LIST OF ABBREVIATIONS

AE	Adverse Event
ANSM	*Agence Nationale de Sécurité du Médicament et des produits de santé* (French medicines agency)
CNAM-TS	*Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* (National healthcare insurance system for salary people)
CNIL	*Commission Nationale Informatique et Libertés*
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EGB	*Echantillon Généraliste de Bénéficiaires* (1/97th representative sample of the national insurance database)
EMA	European Medicines Agency
FDA	Food and Drug Administration
GPRD	General Practice Research Database
LTD	Long-Term disease
MAH	Marketing Authorisation Holder
MSA	*Mutualité sociale agricole* (National healthcare insurance system for farmers)
OAC	Omeprazole-Amoxicillin-Clarithromycin
OTC	Over-The-Counter
PPIs	Proton Pump Inhibitors
PMSI	*Programme de Médicalisation des Systèmes d'Information* (National hospital-discharge summaries database system)
RSI	*Régime Social des Indépendants* (National healthcare insurance system for self-employed workers)
SAP	Statistical Analysis Plan
SNIIR-AM	*Système National d'Information Inter-Régimes de l'Assurance Maladie* (National healthcare insurance system database)
UBT	Urea Breath Test

3 PARTIES INVOLVED IN THE STUDY

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Coordinating centre				
Pr Nicholas Moore **Head of CIC1401**	✓	✓		✓
Dr Patrick Blin **Scientific project leader**	✓	✓		✓
Cécile Droz-Perroteau **Chief operating officer**	✓			
Magali Rouyer **Project manager**		✓		
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Régis Lassalle **Statistician and data manager chief**			✓	
Sponsor				
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Catherine Godefroy **Executive Director, Global Pharmacovigilance & Risk Management**	✓			✓
Ilse Sjoholm **EEA Qualified Person for Pharmacovigilance**				✓

4 ABSTRACT

TITLE	DUS: Drug Usage patternS of Pylera® in France using the national claims reimbursement database.
RATIONAL AND BACKGROUND	The commonly used regimens for the eradication of *Helicobacter pylori* (*H. pylori*) infection consist of the simultaneous administration of proton pump inhibitors (PPIs) and 1 to 3 antimicrobial agents, such as amoxicillin, clarithromycin, metronidazole, fluoroquinolone, and/or tetracycline. Pylera® is a 3-in-1 capsule therapy (for bacteria-causing peptic ulcers) containing bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride. A Marketing Authorisation Application was filed by Aptalis Pharma for Pylera® in Europe (France, Spain, Italy, Germany, Poland, Belgium, Ireland, Portugal, and the United Kingdom) via a decentralised procedure on 29 January 2010. The decentralized procedure ended on July 6, 2011 with a favourable opinion. Pylera® received approval from the French Regulatory Authority, *Agence Nationale de Sécurité du Médicament et des produits de santé* (ANSM), on 16 January 2012 and has been marketed in France since 10 April 2013. In France, several cases of bismuth encephalopathy were reported in the 1970s. This led to the removal of bismuth-containing products from the French market. The ANSM has, therefore, raised some concerns regarding the potential risk of bismuth encephalopathy with Pylera®, a bismuth-containing compound. To address the request of a Drug Utilisation Study in France, the Marketing Authorisation Holder of Pylera® has entrusted the Department of Pharmacology, University of Bordeaux, with the study and the monitoring of the product usage pattern after launch in order to gain reassurance on the safety and usage patterns of this drug in a real-life setting.
RESEARCH QUESTION AND OBJECTIVES	To describe the usage patterns of Pylera® in real-life practice.
STUDY DESIGN	The study design is a prospective, non-interventional, longitudinal and dynamic cohort study using a representative French national claims (EGB) and hospitalisation database of patients with a first dispensation of Pylera® with a follow-up of 2 years, and a one-year history in the database. A reference population is defined using patients with a dispensation of specific tritherapy to eradicate *H. pylori* and the same design. Patients are included for a period of 2 years and analysed after one month of follow-up (description at inclusion), after three months of follow-up (misuse), after one year of follow-up (treatment failure) and after two years of follow-up (recurrence).

	Successive reports are provided taking account the date of each report and the availability of the data.
POPULATION	**Pylera® population** All subjects in the database, with one or more claims of Pylera® at any time starting at the first Pylera® marketing in France, i.e. from April 2013 to March 2015. Subjects should be included in the study only once. Several cohorts are identified from Pylera® post-launch corresponding to all patients with a first Pylera® prescription in the EGB database. It is successive data extractions, each representing an increment of the number of patients included in the preceding cohort, as well as of the follow-up duration. Consequently, each successive and incremental cohort will be described using information available at the time of data extraction. **Reference population** The reference population is a cohort of patients who have a dispensation of a specific tritherapy to eradicate *H. pylori* during the same period.
VARIABLES	**Index date:** The index date is defined as the date of the first dispensation of Pylera® for the Pylera® population and, as the date of the first dispensation of specific tritherapy to eradicate *H. pylori* for the reference population, during the study inclusion period. **Evaluation criteria:** According to the availability of data in the database, the main evaluation criteria are defined as follows: • number of drug packs of Pylera® dispensed per patient and per year; • misuse at index date: dispensation of more than one pack of Pylera® at index date or a dispensation of Pylera® not preceded by UBT or endoscopy (within the year before first dispensation); • normal use at index date: patient without misuse at index date; • treatment failure: dispensation of a second pack of Pylera® or of another *H. pylori* eradication drug combination after or not UBT or endoscopy in the 12 months following first dispensation of Pylera®; • treatment of recurrent infection: dispensation of a new pack of Pylera® or of another drug combination for *H. pylori* eradication after or not UBT or endoscopy more than 12 months after the last dispensation of Pylera®. The second evaluation criteria are the following: • concomitant medication, healthcare usage; • presence of hospitalisation via the *Programme de Médicalisation des Systèmes d'Information* (PMSI); • duration of treatment as assessed by the number of packs

	dispensed, each counting for 10 days of treatment; • total quantity of bismuth subcitrate potassium dispensed per patient. **Prescriber characteristics, Patients characteristics, medical history and pattern of Pylera® use:** The following data are extracted: • characteristics of the prescribers: medical specialty, type of activity; • demographic characteristics of the users: age, gender, place of residence, socioeconomic status distribution; • dispensed dose of Pylera®, number of dispensations over the study period, concomitant dispensation; • recent and current history of drug dispensation and procedures; • concomitant use of another drug: omeprazole and other PPIs, delivery of OAC or other specific tritherapy to eradicate *H. pylori* before or after Pylera®; • profile of medical acts prescriptions and consultations; • long-term disease (LTD) description; • hospitalisation diagnoses; • vital status at the end of follow-up; • neurological consultation and procedures suggestive of encephalopathy; • if possible and according to specific French recommendation: off-label use description (e.g., for FDA: pregnant or nursing women, paediatric patients, and patients with hepatic or renal impairment should not receive this combination therapy); hepatic or renal impairment will be derived from the LTD list; other diagnoses such as pregnancy from specific pregnancy markers in the database.
DATA SOURCES	The EGB is a permanent and representative 1/97 random sample of the national healthcare insurance database linked to the national hospital-discharge summary database (PMSI) and the national death registry using a unique pseudonymised identifier. It contains the longitudinal records of more than 700 000 subjects, whether or not they had a claim since 2003.
STUDY SIZE	All subjects in the database with one or more claims of Pylera® will be included. According to the estimated sales data of Pylera®, we expect approximately 50 000 patients treated by Pylera® during the 3-year inclusion period in SNIIR-AM and 500 patients in the EGB.
DATA ANALYSIS	The main analysis is a description of patient characteristics in the study and the reference populations, as well as the number of drug packs dispensed per patient, misuse, treatment failure and recurrence of infection for the Pylera® population.

MILESTONES	• Drafting of study protocol and SAP.	Q4 2011 – Q2 2013

	• Definition and validation of EGB data extraction. • Annual interim study report provided to the ANSM	Q2 2014 – Q2 2015
	• Preliminary final study report provided to the ANSM	Q2 2016
	• Consolidated final study report provided to the ANSM	Q1 2017

5 AMENDMENTS AND UPDATE

Number	Date	Section of study protocol	Amendment or update	Reason
1	9/12/2014	7	Additional information to clarify the introduction and background.	Clarifications in the study protocol
		8	Additional information to clarify the objectives.	Clarifications in the study protocol
		9.2	Table 1 added to identify the different cohorts according to the follow-up and annual reports sent to ANSM.	Clarifications in the study protocol
		9.3	Additional information to clarify index date and study period for data analysis.	Clarifications in the study protocol
		9.4	Additional information to clarify data source and specificity of EGB database	Clarifications in the study protocol
		9.5	Additional information to clarify the study size	Clarifications in the study protocol
		11	Update according to the last revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) from EMA (coming into effect 16 Sept 2014)	
		13	Update of references	
2	20/01/2016	2	Update of the list of abbreviations	
		3	Update of the project team and sponsor contacts involved in the study	Changes in the organisation of the different parties involved
		4	Update tacking into account changes specified in the following sections	
		6	Update of the timelines of annual reports submission to the ANSM tacking into account the availability of data in Health databases. Deletion of the timelines for internal reports provided to MAH.	
		6	Removal of SNIIR-AM extraction	Not applicable due to sufficient number of patients in EGB database
		9.1	Main criteria deleted and specified in the section 9.3	Clarifications in the study protocol
		9.2	Inclusion period added for each cohort identified. Table 1 moved to the section 9.7.	Clarifications in the study protocol
		9.3	Additional information to clarify the main criteria. Data recorded in EGB added to clarify the	Clarifications in the study protocol

			variables used for the description. Additional information to clarify the description of concomitant use of another drug before or after Pylera®.	
		9.4	Removal of SNIIRAM data source	Not applicable due to sufficient number of patients in EGB database
		9.4	Clarification of the main data available in EBG database.	Clarifications in the study protocol
		9.7	Table 1 updated taking into account the availability of data in Health databases described in preliminary and consolidated final reports with deletion of 3-month follow-up and Cohorts 2 and 4.	Clarifications in the study protocol: Cohort 2 and Cohort 4 were developed to prepare interim reports for inclusion in the 6-monthly PSURs. The follow-up of these cohorts has not been pursued due to the lack of data regarding main outcome criteria at the time of data extraction for final reports. Consequently, Cohorts 2 and 4 as well as 3-month follow-up were not retained for final reports sent to Regulatory authorities
		12	Update of the submission report period to the regulatory authorities Additional information concerning the adherence to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) Code of Conduct.	Specific agreement signed by the parties involved in the study

6 MILESTONES

Milestones	Planned Date
• Drafting of study protocol and SAP. • Definition and validation of EGB data extraction.	Q4 2011 – Q2 2013
• Annual interim study report provided to the ANSM.	Q2 2014 – Q2 2015
• Preliminary final study report provided to the ANSM. • Consolidated final study report provided to the ANSM.	Q2 2016 Q1 2017

7 RATIONALE AND BACKGROUND

The commonly used regimens for the eradication of *Helicobacter pylori* (*H. pylori*) infection consist of the simultaneous administration of proton pump inhibitors (PPIs) and 1 to 3 antimicrobial agents, such as amoxicillin, clarithromycin, metronidazole, fluoroquinolone, and/or tetracycline.

Pylera® received approval from the Food and Drug Administration (FDA) on 28 September 2006, and was launched in the United-States in May 2007. Pylera approval has also been granted in Kuwait on April 7, 2011 and launched in Kuwait in April 2011. Pylera® is a 3-in-1 capsule therapy (for bacteria-causing peptic ulcers) containing bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride. Pylera® is prescribed in USA and Kuwait in combination with omeprazole for the eradication of *H. pylori* and prevention of relapse of duodenal ulcers in patients with a known history of (within the past 5 years) or active *H. pylori*-associated ulcers.

A Marketing Authorisation Application was filed by Aptalis Pharma (formerly known as Axcan Pharma) for Pylera® in Europe (France, Spain, Italy, Germany, Poland, Belgium, Ireland, Portugal, and the United Kingdom) via a decentralised procedure on 29 January 2010. The decentralized procedure ended on July 6, 2011 with a favourable opinion. Pylera® received approval from the French Regulatory Authority, *Agence Nationale de Sécurité des Médicaments et des produits de Santé* (ANSM), on 16 January 2012 and has been marketed in France since 10 April 2013.

In two Phase 3 studies, treatment with Pylera® achieved *H. pylori* eradication rates ranging between 84 and 97%; demonstrating it is considered an effective first-line therapeutic option[1].

During clinical trials conducted in North America and Europe with Pylera® and omeprazole, which included a total safety population of 540 subjects, the reported Adverse Events (AEs) were consistent with the known safety profiles of the components of Pylera®. Gastrointestinal disorders were the most commonly reported AEs.

In France, several cases of bismuth encephalopathy were reported in the 1970s, which were associated with the chronic use of high doses of bismuth for chronic gastrointestinal disorders such as irritable bowel syndrome or chronic gastritis, leading to high bismuth concentrations and bismuth accumulation (high blood levels and a direct link between the amount of bismuth present in the cerebrospinal fluid and severity of clinical manifestations)[2]. This led to the removal of bismuth-containing products from the French market. The ANSM, has, therefore, raised some concerns regarding the potential risk of bismuth encephalopathy with Pylera®, a

bismuth-containing compound. To date, there have been no clinical trial reports or postmarketing safety reports of bismuth encephalopathy with Pylera®.

The Marketing Authorisation Holder (MAH) anticipates the potential risk of bismuth encephalopathy would be increased in the setting of overdose or chronic use of Pylera®. Repeat prescription of Pylera® might be justified by an initial treatment failure in case of non-eradication of *H. pylori* after Pylera® treatment because of drug resistance, non-compliance or interactions with others drugs or food. The potential benefits of bismuth on gastrointestinal symptoms unrelated to *H. pylori* infection may also lead to repeat prescriptions of Pylera®.

The main marker of such misuse would be the repeat prescription or dispensation of Pylera®, with or without indication of an *H. pylori* diagnosis or eradication failure.

This misuse may be identified using dispensation or reimbursement databases, to quantify the number of users, individual patient dispensation patterns, and the quantities dispensed per patient. Such data would help to quantify individual risk or the emergence of potentially at-risk behaviour. Patients receiving one single dispensation, or at most a second dispensation in the case of initial treatment failure, would not be considered at increased risk of bismuth encephalopathy.

To address the request of a Drug Utilisation Study in France, the MAH of Pylera® has entrusted the Department of Pharmacology, University of Bordeaux, with the study and the monitoring of the product usage pattern after launch in order to gain reassurance on the safety and usage patterns of this drug in a real-life setting.

This study Protocol is drafted according to the template recommended by the European Medicines Agency (EMA) (http://www.ema.europa.eu) in accordance with the procedures in the Pharmacology Department.

8 RESEARCH QUESTION AND OBJECTIVES

The objective of the study is to describe the usage patterns of Pylera® in real-life practice by obtaining the following data: prescribers; patient age; patient gender; dispensed dose and quantity; number of dispensations over the study period; and concomitant medications dispensing (in particular, of all PPIs).

9 RESEARCH METHODS

9.1 STUDY DESIGN

The study design is a prospective, longitudinal and dynamic cohort study using a representative national French reimbursement database entitled the *Echantillon Généraliste des Bénéficiaires* (EGB), which is a 1/97th sample of SNIIR-AM (*Système National d'Information Inter-Régimes de l'Assurance Maladie*) and hospitalisation database of patients with a first dispensation of Pylera® with a follow-up of 2 years, and a one-year history in the database.

This study is a non-interventional study and there will be no interaction between the MAH and the prescribers whatsoever, therefore the study has no influence on the prescribing of Pylera®, other specific tritherapy to eradicate *H. pylori* or any diagnostic or monitoring procedures.

A reference population is defined using patients with a dispensation of specific tritherapy to eradicate *H. pylori* and the same design.

Patients are included for a period of 2 years and analysed after one month of follow-up (description at inclusion), after three months of follow-up (misuse), after one year of follow-up (treatment failure) and after two years of follow-up (recurrence).

Successive reports are provided taking account the date of each report and the availability of the data.

9.2 SETTING AND STUDY POPULATION

9.2.1 Setting

The study is performed in a real-life setting with patients identified and followed-up in a claims and hospitalisations database: EGB and the *Programme de Médicalisation des Systèmes d'Information* (PMSI, the hospitalisation database).

9.2.2 Study population

Several cohorts will be identified from Pylera® post-launch corresponding to all patients with a first Pylera® prescription in the EGB database, starting at the first Pylera® marketing in France, i.e. from April 2013 to March 2015. It is successive data extractions, each representing an increment of the number of patients included in the preceding cohort, as well as of the follow-up duration. Tacking into account the submission date of the annual study reports to the ANSM, the inclusion period of each cohort is as follows:

- Cohort 1: 01 April 2013 to 30 June 2013,
- Cohort 3: 01 April 2013 to 30 April 2014,
- Cohort 5: 01 April 2013 to 31 March 2015.

Cohort 2 and Cohort 4 were developed to prepare interim reports and these two cohorts are not described in final report to Regulatory authorities.

Pylera® population

The Pylera® population corresponds to all subjects in the EGB database with one or more claims of Pylera® at any time in the French databases starting at the time of first Pylera® marketing in France. Subjects should be included in the study only once.

The Pylera® population is selected from the patients present in the EGB as follows:

- all patients in the database with at least one reimbursement of Pylera® (***Club Inter Pharmaceutique***, CIP, code=2180420, Anatomic/Therapeutic/Chemical, ATC code=A02BD08) from 01 April to the nearest month having available data with completion rate of at least 98.3% in the EGB (at the time of extraction);
- with data in the EGB for a follow-up period of at least one year before and one year after the date of first Pylera® dispensation (for this study report);
- and being permanently affiliated to a health scheme included in the EGB (*Régime Général*, RG, *Mutualité Sociale Agricole*, MSA, and *Régime Social des Indépendants*, RSI) during the study period.

Reference population

The reference population is defined as patients with at least one reimbursement of one of the following specific tritherapy to eradicate *H. pylori* during the same period as the Pylera® population:

- either in fixed combinations:
  - omeprazole, amoxicillin, and metronidazole (ATC code A02BD01),
  - lansoprazole, tetracycline, and metronidazole (ATC code A02BD02),
  - lansoprazole, amoxicillin, and metronidazole (ATC code A02BD03),
  - pantoprazole, amoxicillin, and clarithromycin (ATC code A02BD04),
  - omeprazole, amoxicillin, and clarithromycin (ATC code A02BD05),
  - esomeprazole, amoxicillin, and clarithromycin (ATC code A02BD06),

- lansoprazole, amoxicillin, and clarithromycin (ATC code A02BD07).

- or individually prescribed at the same time:
  - two or more antibiotics among: amoxicillin (ATC code J01CA04) - clarithromycin (ATC code J01FA09) - metronidazole (ATC code J01XD01, P01AB01) - tetracycline (ATC code J01AA07),
  - at least one PPI among: omeprazole (ATC code A02BC01) - pantoprazole (ATC code A02BC02) - lansoprazole (ATC code A02BC03) - esomeprazole (ATC code A02BC05);
- with data in the EGB for a follow-up period of at least one year before and one year after the date of first specific tritherapy dispensation (for this study report);
- and being permanently affiliated to a health scheme included in the EGB (*Régime Général*, RG, *Mutualité Sociale Agricole*, MSA, and *Régime Social des Indépendants*, RSI) during the study period.

Patients with both STT and Pylera® dispensation during the inclusion periods will be included only in the Pylera® population.

9.3 VARIABLES

9.3.1 Index date

The index date is defined as the date of the first dispensation of Pylera® for the Pylera® population and as the date of the first dispensation of specific tritherapy to eradicate *H. pylori* for the reference population, during the study inclusion period.
Because there is no information in the EGB regarding the duration of treatment, theoretical treatment period is defined as:

- 10 days after the index date for the Pylera® population,
- 14 days after the index date for the reference population (specific tritherapy to eradicate *H. Pylori*).

9.3.2 Outcomes

Main outcomes

According to the availability of data in the database, the evaluation criteria is defined as follows:

- **Number of drug packs dispensed per patient and per year**,
- **Misuse at index date**: dispensation of more than one pack of Pylera® at index date or a dispensation of Pylera® not preceded by urea breath test (UBT) or endoscopy (within the year before first dispensation),
- **Normal use at index date**: patient without misuse at index date,
- **Treatment failure**: dispensation of a second pack of Pylera® or of another *H. pylori* eradication drug combination after or not UBT or endoscopy in the 12 months following first dispensation of Pylera®,
- **Treatment of recurrent infection**: dispensation of a new pack of Pylera® or of another drug combination for *H. pylori* eradication after or not UBT or endoscopy 12 months or more after the last dispensation of Pylera®.

Secondary outcomes

Other criteria will be assessed to describe the usage patterns of Pylera® in real-life practice with French databases:

- concomitant medication, healthcare usage;
- presence of hospitalisation via the *Programme de Médicalisation des Systèmes d'Information* (PMSI);
- duration of treatment as assessed by the number of packs dispensed, each counting for 10 days of treatment;
- total quantity of bismuth subcitrate potassium dispensed per patient.

9.3.3 Prescriber characteristics of *H. pylori* eradication treatments

The main characteristics of prescribers will be the medical specialty and type of activity (private/public).

9.3.4 Demographic characteristics of patients

The demographic characteristics of patients will be described as follows:

- Gender, age, and *Couverture Maladie Universelle complémentaire* (CMUc, full coverage for socially deprived people) (at the index date);
- Geographical region of residence.

9.3.5 Medical history of patients

The medical history will be described in the 12 months preceding index date as follow:

- History of long-term diseases (LTD): LTD declared or ongoing, type of LTD and associated ICD-10 codes;
- History of UBT and endoscopies performed (hospital and non-hospital exams);
- History of dispensation of specific treatment to eradicate *H. pylori*: associations between PPIs and antibiotics defined in section 9.2.2 for specific tritherapy, and other associations of PPIs and antibiotics for non-specific tritherapy;
- History of dispensation of other drugs: dispensations of other drugs according to CIP and ATC codes;
- History of hospitalisations and diagnoses;
- History of medical visits and physician specialty.

9.3.6 Pattern of Pylera® use at index date and during follow-up period

Pattern of Pylera® use will be described at index date and during the follow-up period as follows:

- Conditions of Pylera® dispensation: number of packs, number of dispensations, and total quantity of bismuth subcitrate potassium dispensed;
- Specific population at index date: pregnant or nursing women, paediatric patients, and patients with hepatic or renal impairment;
- UBT and endoscopies performed;
- Dispensation of specific treatment to eradicate *H. pylori*: associations between PPIs and antibiotics defined in section 9.2.2 for specific tritherapy, and other associations of PPIs and antibiotics for non-specific tritherapy;

- Dispensation of other drugs: dispensations of other drugs according to CIP and ATC codes;
- Hospitalisations and diagnoses;
- Vital status at the end of follow-up;
- Medical visits and physician specialty, notably neurological consultation and procedures suggestive of encephalopathy.
- if possible and according to specific French recommendation: off-label use description (e.g., for FDA: pregnant or nursing women, paediatric patients, and patients with hepatic or renal impairment should not receive this combination therapy); hepatic or renal impairment will be derived from the LTD list; other diagnoses such as pregnancy from specific pregnancy markers in the database.

The descriptive analysis of the reference population will be identical to their associated Pylera® population during treatment period and the periods preceding and following index date (other than dispensation of Pylera®).

9.4 DATA SOURCES

The EGB is a permanent and representative 1/97th sample of the national healthcare insurance database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*, SNIIRAM) linked to the national hospital-discharge summary database (PMSI) and the national death registry using a unique pseudonymised identifier.. The EGB currently includes more than 700 000 patients from the 3 main healthcare insurance systems (RG of the CNAM-TS except civil servants and students, MSA, and RSI), which represent 87% of the French population. The EGB, the process of drug prescription, drug delivery, and recording of medical data in the French health system are described in a recent publication[3]. The EGB is representative of the French population in terms of gender, age, and mean individual expenditure reimbursed. Non-hospital healthcare data are available since 2003 for the *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* (CNAM-TS), and 2011 for the MSA and the RSI. Hospital discharge information is available since 2005 for the CNAM-TS, and 2010 for the MSA and RSI populations. Non-hospital data are updated every month (6 months to include about 98.3% of the healthcare used and one year to reach 99.9% of data completion) and hospital discharge summaries yearly at end of the third quarter (Q3) for the previous year.

The EGB sample has been made available to authorised sites for pharmacoepidemiologic research. The INSERM Pharmacoepidemiology CIC Bordeaux CIC1401 research unit

(Bordeaux PharmacoEpi) is authorised to access EGB directly, and SNIIR-AM through the CNAM-TS (*arrêté du 20 juin 2005 relatif à la mise en oeuvre du système national d'information inter-régimes de l'assurance maladie, paru au Journal Officiel du 19 août 2005*).

If there are any concerns regarding results at any time, an action plan will be discussed with the ANSM and exploration of databases of other countries (such as Germany with the LandernKassen database, the United Kingdom with the General Practice Research Database (GPRD), Italy with the Health Search Database, or regional databases) may be conducted.

Main data available are:

- General characteristics: gender, year of birth, CMU-c (a social status), affiliation scheme (RG, MSA, RSI), department of residence, date of death (month and year, for those concerned),
- Long-term diseases (LTD) registration with full insurance coverage (*Long-Term Disease* and their associated International Classification of Diseases – 10th Revision, ICD-10 codes) with start and end date of LTD,
- Outpatient reimbursed healthcare expenditures with dates (prescription and execution), prescriber and professional caregiver information (medical or paramedical specialty, private/public practice) and code (but not the corresponding medical indication nor result): visits and medical procedures, laboratory tests, drugs and medical devices,
- Hospital discharge summaries from the PMSI: ICD-10 diagnosis codes (main, related, and associated diagnosis) for all medical, obstetric and surgery hospitalisations with the date and duration of hospitalisation, medical procedures, hospitalisation department, and cost coding system.

Over-The-Counter (OTC) drugs or non-reimbursed prescription drugs are not in the database, only reimbursed items are included. The reimbursement claims are submitted when the prescription is filed at a pharmacy.

9.5 STUDY SIZE

In the EGB, 568 patients were identified in 2010 as having had an UBT or another specific diagnostic test related to *H. pylori* infection, and having received a simultaneous dispensation of OAC or a similar treatment combination. Regarding only simultaneous OAC dispensation, 406 patients had a diagnostic test for *H. pylori*, 179 of whom also had an endoscopy. A further 595 had co-dispensation of OAC without *H. pylori* diagnostic tests, 308 of whom underwent an

endoscopy. This represents between 487 and 1100 patients apparently treated for eradication of *H. pylori*, i.e. 50 000 to 100 000 patients nationally.

According to the projected sales of Pylera® in France and based on the potential patients identified in EGB, the number of patients newly exposed to Pylera® will be approximately 70 the first year after launch, 140 patients the 2nd year, and 270 patients the 3rd year. Sales data will be used to compute the expected number of patients exposed to Pylera® in the EGB, and analysis dates may be modified accordingly.

The 70 patients in the EGB in the first year represent a reasonable estimate of a 7 to 14% market penetration.

Therefore all subjects in the database with one or more claims of Pylera® will be included. We expect approximately 50 000 patients treated by Pylera® during the 3-year inclusion period in SNIIR-AM and 500 patients in the EGB.

9.6 DATA-MANAGEMENT

Database extraction criteria will be fully described in a Data Extraction Plan (DEP) approved prior to initiating extraction.

9.7 DATA ANALYSIS

The statistical analyses will be carried out for each interim report and final report by the Department of Pharmacology according to a documented and approved Statistical Analysis Plan (SAP). The SAP describes the statistical analyses as foreseen at the time of planning the study.

For each report, statistical analysis will be performed after each database extraction from EGB using SAS® software (SAS Institute, last version, North Carolina, USA). Blind double programming will be used for the main outcome measures.

Qualitative variables (dichotomous or categorical) will be described in terms of number and frequency. Quantitative variables will be described in terms of mean, standard deviation, median, first and third quartiles.

Descriptive statistics of population included in the study, including patient demographics, prescribers, concomitant medication, usage patterns of Pylera® and evolution over time will be carried out.

Each successive and incremental cohort will be described using information available at the time of data extraction. Annual interim reports will be sent to the French regulatory authority (ANSM) and German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte* (BfArM)) (Table 1).

Table 1: Description of cohorts according to the follow-up and milestones of report submission.

Deadline for report submission*	**Follow-up**		
	1 month	**12 months**	**24 months**
Interim report: Apr. 2014	Cohort 1		
Interim report: Jun. 2015	Cohort 3	Cohort 1	
Preliminary final report*: Jun. 2016	Cohort 5	Cohort 3	Cohort 1
Consolidated final report*: Mar. 2017	Cohort 5	Cohort 3	Cohort 1

** Preliminary final report: results based on data without 2015 hospital information; Consolidated final report: results based on data with 2015 hospital information.*

The preliminary final study report dated June 2016 will be described the subsequent cohort with data completion rate of at least 98.3%:

- Cohort 5 will correspond to the larger cohort and will be used to describe the 1-month follow-up period and during the pre-treatment period.
- Cohort 3 with less patients than cohort 4 and will be used to describe the populations at 12 months of follow-up (cross-sectional),
- Cohort 1 with small number of patients and will be used to describe the populations at 24 months of follow-up (cross-sectional).

A consolidated final study report will allow describing an update of preliminary final results, based on data with 2015 hospital information.

9.8 QUALITY CONTROL

The Department of Pharmacology has a quality system with Standard Operative Procedures for all its activities, especially programming, database management, statistical analysis and report.

In order to avoid programming error for the main evaluation criterion, two statisticians will do independently the programming of exposure, frequency of exposure, and secondary efficacy and safety endpoints.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Strength: The SNIIR-AM is a national healthcare claims database linked to the national hospital discharge summaries that cover more than 90% of the French population. It provides a unique opportunity to identify all patients treated by Pylera®. The database is considered as fully representative of the French population. The EGB is a 1/97th random sample of SNIIR-AM.

Furthermore, the SNIIR-AM and EGB has the advantages of any study extracting patients' records from an existing database. It collects data that are not impacted by study conduct, especially when dealing with physician's prescribing behaviours. In addition, due to its initial purpose, it contains exhaustive information about treatments and utilization of reimbursed healthcare resources.

Selection bias: Since all patients identified with a dispensation of Pylera® will be extracted from a national database, there is no study selection bias, nor attrition bias.

Information bias: Since deaths are recorded in the database using the national death registry, there is no information bias. Moreover, hospitalisation will be defined using the discharge diagnosis coded in the database from which serious AEs requiring hospitalisation can be identified. The PMSI coding is fully independent from the study and there is no reason that the potential miscoding will be different for Pylera®-treated patients in comparison with non-Pylera®-treated patients, excluding such information bias.

9.10 OTHER ASPECTS

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

This project is a database analysis using anonymous individual information, with the authorisation of the French Data Privacy Commission (CNIL).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The last revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) from EMA (coming into effect 16 Sept 2014) precises: "In accordance with ICH-E2A (see GVP Annex IV), the definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, as detailed in ICH-E2D (see GVP Annex IV), if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded".

For Non-interventional post-authorisation studies based on secondary use of data (VI.C.1.2.1.b): The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the reporting of suspected adverse reactions in the form of ICSRs is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting.

This project is a database analysis using anonymous individual information without any spontaneous reporting. Study endpoints will be reported in aggregate in the final study report, and no individual or expedited reporting is required, according the EMA Guideline on good pharmacovigilance practices cited above (GVP IV), as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

12 PLAN FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The annual study reports will be sent to the regulatory authorities between 2014 and 2017.

A specific agreement stating adherence to the rules of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct in their entirety has been signed by the parties. For publication, the ENCePP chart will apply. Publications will follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and follow Uniform Requirements of Manuscripts Submitted to Biomedical Journals (http://www.icmje.org).

13 REFERENCES

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3. Martin-Latry K, Begaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! Pharmacoepidemiol Drug Saf. Mar;19(3):256-65