CENTRE HOSPITALIER ET UNIVERSITAIRE DE BORDEAUX
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UNIVERSITE BORDEAUX SEGALEN

SERVICE DE PHARMACOLOGIE
CIC-P 0005 PHARMACO-EPIDEMIOLOGIE

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

Study Protocol V3.1
26 April 2013

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PASS INFORMATION

Title	DUS: Drug Usage patternS of Pylera® in France using the national claims reimbursement database
Protocol version	V3.1
Date of last version of protocol	26 April 2013
EU PASS register number	On-going
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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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

AE	Adverse Event
ALD	Affection de Longue Durée
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
CNAM-TS	Caisse Nationale d'Assurance Maladie des Travailleurs Salariés
CNIL	Commission Nationale Informatique et Libertés
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EGB	Echantillon Généraliste de Bénéficiaires
FDA	Food and Drug Administration
GPRD	General Practice Research Database
IDS	Institut des Données de Santé
MAH	Marketing Authorisation Holder
MSA	Mutualité sociale agricole
OAC	Omeprazole-Amoxicillin-Clarithromycin
OTC	Over-The-Counter
PPIs	Proton Pump Inhibitors
PMSI	Programme de Médicalisation des Systèmes d'Information
RMS	Reference Member State
SAP	Statistical Analysis Plan
SNIIR-AM	Système National d'Information Inter-Régimes de l'Assurance Maladie
RSI	Régime Social des Indépendants
UBT	Urea Breath Test

3 RESPONSIBLE PARTIES

PROJECT TEAM

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4 ABSTRACT

TITLE	DUS: Drug Usage patternS of Pylera® in France using the national claims reimbursement database.
Protocol version	V3.1
Date of protocol	26 April 2013
Main author	Dr Patrick Blin, INSERM CIC-P 0005, Service de Pharmacologie, Université Bordeaux Segalen, Bordeaux, France.
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. 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 French Regulatory Authority, *Agence Nationale de Sécurité du Médicament et des produits de santé (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 Bordeaux Segalen, 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 cohort study using the full national French reimbursement database.
POPULATION	All subjects in the 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 index date is defined by the date of the first-ever recorded dispensing of Pylera®. This may correspond to a first dispensing or to a renewed

	prescription if the first dispensing was in hospital. The study period is defined as the 12 months preceding and the 12 months following the index date. Study subjects will be identified 6 then 12 months post-launch. The study will be conducted for at least one year from the launch of Pylera® reimbursement in France, and renewable as needed to accrue a sufficient number of Pylera®-treated subjects.
VARIABLES	The following data will be extracted: • demographic characteristics of the users: age, gender, place of residence, socioeconomic status distribution; • characteristics of the prescribers; • delivered dose of Pylera®, frequency of dispensing, concomitant dispensing; • recent and current history of drug dispensation and procedures; • concomitant use of another drug: omeprazole and other PPIs, delivery of OAC before or after Pylera®; • profile of medical acts prescriptions and consultations; • long-term disease (ALD) 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 ALD list; other diagnoses such as pregnancy from specific pregnancy markers in the database.
DATA SOURCES	The SNIIR-AM database is a national healthcare insurance system database with individual anonymous information about exhaustive non-hospital reimbursed claims linked to the national hospital-discharge summaries database system (PMSI), and covers currently more than 90% of the French population. The EGB is a representative 1/97 sample of all three major insurance programs (CNAM-TS, MSA, RSI, i.e., 87% of the general population). It contains the longitudinal SNIIRAM records of 670 000 patients, whether or not these individuals have made a reimbursement 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.
STATISTICAL ANALYSIS	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.

MILESTONES	• Drafting of study protocol and SAP. • Definition and validation of EGB data extraction. • Request for extraction from SNIIR-AM database if necessary.	Q4 2011 – Q2 2013
	• Regular internal reports at 6-monthly intervals. • An interim report to the ANSM at one year, and full reports at 2 and 3 years. • If necessary, at the time of the interim report, a futility analysis with overall Pylera® sales: if within the first analysis period Pylera® sales are lower than expected and therefore only the SNIIR-AM database will be considered. • Confirmation of request for extraction from SNIIR-AM database if number of patients in the EGB is insufficient.	Q2 2013 – Q2 2016
	• Final report	Q22016

5 AMENDMENTS AND UPDATE

Number	Date	Section of study protocol	Amendment or update	Reason

Not applicable.

6 MILESTONES

Milestones	Planned Date
• Drafting of study protocol and SAP. • Definition and validation of EGB data extraction. • Request for extraction from SNIIR-AM database if necessary.	Q4 2011 – Q2 2013
• Regular internal reports will be available at 6-monthly intervals. • An interim report will be provided to the ANSM at one year, and full reports at 2 and 3 years. • At the time of the interim report, a futility analysis will be done with overall Pylera® sales: if within the first analysis period Pylera® sales are lower than 7000 packs nationally, then the expected number of 70 patients in the EGB will not be met and therefore only the SNIIR-AM database will be considered for further extractions, analysis, and reports of French databases. Of note, Pylera® sales will be regularly monitored to estimate the	Q2 2013 – Q2 2016

expected power of the EGB analysis, and the timing of interim analyses. • Confirmation of request for extraction from SNIIR-AM database if number of patients in the EGB is insufficient.	
• Final report.	Q2 2016

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.

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, associated with the chronic use of high doses of bismuth, leading to high bismuth concentrations and bismuth accumulation. This led to the removal of bismuth-containing products from the French market. The French Regulatory Authority, *Agence Nationale de Sécurité du Médicament et des produits de santé (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 initial treatment failure in case of non-eradication of *H. pylori* after Pylera® treatment because of drug resistance or non-compliance or interactions with others drugs or food. The potential benefits of bismuth on gastrointestinal symptoms unrelated to *H. pylori* infection, such as irritable bowel disease or chronic gastritis – which were the therapeutic indications for the high-dose long-term use of bismuth associated with encephalopathies – may also lead to repeat prescriptions for 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, which 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 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 Bordeaux Segalen, 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.

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; age; gender; delivered dose; frequency of dispensing; treatment duration; and concomitant medications dispensing (in particular, of all PPIs).

9 RESEARCH METHODS

9.1 STUDY DESIGN

The study design is a prospective, longitudinal cohort study using the full national French reimbursement database entitled *Système National d'Information Inter-Régimes de l'Assurance Maladie* (SNIIR-AM) and the *Echantillon Généraliste des Bénéficiaires* (EGB), which is a 1/97 sample of SNIIR-AM.

This study is a non-interventional study. Since there will be no interaction with the prescribers whatsoever, there will be no risk of the study influencing the prescribing of Pylera® or any diagnostic or monitoring procedures.

The main evaluation criterion used to explore French databases will be the number of dispensed drug boxes per patient and per year. In case of two or more than two dispensations for a same patient, the duration in between will be analysed.

Pylera® use will be classified in the following manner:

- normal use: dispensation of one pack only, preceded or followed or not by a second Urea Breath Test (UBT), with or without endoscopy;
- misuse: dispensation of a pack not preceded by UBT or endoscopy; dispensation of more than one pack without UBT or endoscopy between dispensations;
- treatment failure: dispensation of a second pack of Pylera® or of another *H. pylori* eradication drug combination after UBT or endoscopy following initial dispensation of Pylera® and estimation of time between two dispensations to differentiate treatment failure (in the 12 months following first dispensation of Pylera®) and recurrence (beyond the first year after initial dispensation of Pylera®);
- treatment of recurrence infection: dispensation of a second pack of Pylera® or of another drug combination for *H. pylori* eradication after UBT or endoscopy after 12 months following initial dispensation of Pylera®.

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

- concomitant medication, healthcare usage;
- indicators of lack of efficacy with treatment failure and re-medication with Pylera® or Omeprazole-Amoxicillin-Clarithromycin (OAC) triple therapy;
- indicators of safety and serious AEs with 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 dispensed per patient.

All patients with a claim for a UBT and/or an *H. pylori* diagnostic test along with endoscopy and/or OAC triple therapy as described above will be identified during the same period, irrespective of Pylera® treatment. This will permit an estimation of the proportion of the target population treated with Pylera®. The treatment of non-Pylera®-treated patients will be described,

and characteristics and follow-up data for Pylera®- and non-Pylera®-treated patients will be compared.

9.2 SETTING

The study population will include all subjects in the database with one or more claims of Pylera® at any time in the French databases (SNIIR-AM and EGB) starting at the time of first Pylera® marketing in France. Subjects should be included in the study only once. These subjects will form the study cohort.

This is therefore a prospective cohort including patients as they are prescribed Pylera® in the future, to collect data almost in real-time.

In EGB, 568 patients were identified in 2010 as having had an UBT or another specific diagnostic test related to *H. pylori* infection, and 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 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 EGB, and analysis dates may be modified accordingly.

The 70 patients in the first year represent a market penetration of 7 to 14%, which appears to be a reasonable estimate.

The index date is defined by the date of the first-ever recorded dispensing of Pylera®. This may correspond to a first dispensing or to a renewed prescription if the first dispensing was in hospital. The study period is defined as the 12 months preceding and the 12 months following the index date.

Study subjects will be identified 6 then 12 months post-launch. The study will be conducted for at least one year from the launch of Pylera® reimbursement in France, and renewable as needed to accrue a sufficient number of Pylera®-treated subjects.

9.3 VARIABLES

Data analysis will consist in a description of the usage pattern of Pylera®:

- demographic characteristics of the users: age, gender, place of residence, socioeconomic status distribution;
- characteristics of the prescribers;
- delivered dose of Pylera®, frequency of dispensing, concomitant dispensing;
- recent and current history of drug dispensation and procedures;
- concomitant use of another drug: omeprazole and other PPIs, delivery of OAC before or after Pylera®;
- profile of medical acts prescriptions and consultations;
- long-term disease (ALD) 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 ALD list; other diagnoses such as pregnancy from specific pregnancy markers in the database.

9.4 DATA SOURCES

The SNIIR-AM database is a national healthcare insurance system database with individual anonymous information about exhaustive non-hospital reimbursed claims linked to the national hospital-discharge summaries database system (PMSI), and covers actually more than 90% of the French population.

The EGB is a representative 1/97 sample of all three major insurance programs (CNAM-TS, MSA, RSI, i.e., 87% of the general population). It contains the longitudinal SNIIR-AM records of 670 000 patients, whether or not these individuals have made a reimbursement claim since 2003. 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[2]. The EGB sample has been made available to authorised sites for pharmacoepidemiologic research. The Bordeaux Pharmacoepidemiology Unit is authorised to access EGB directly, and SNIIR-AM though 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*).

The access to the SNIIR-AM is regulated and needs approval from the *"Institut des Données de Santé"* (IDS, Institute of health Data) and the *"Commission Nationale Informatique et Libertés"* (CNIL, the French data protection commission).

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.

These are the data recorded in SNIIR-AM and EGB:

- demographic characteristics of the users (age, gender, place of residence, and socioeconomic status);
- prescriber characteristics;
- laboratory and radiology data (in particular for UBT): the name of the test prescribed and reimbursed, the date prescribed, and the date of the results (but not the results themselves);
- drug dispensation characteristics for reimbursements from community pharmacies: name, dose and number of units dispensed (including generic drugs);
- all reimbursed medical procedures prescriptions such as ultrasound, bronchoscopy, upper gastrointestinal endoscopy, etc.;
- all reimbursed medical consultation;
- diagnostic information on selected ALD that qualify the patient for full (100%) reimbursement of all related medical expenses;
- vital status.

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.

Since April 2011, information concerning hospital admissions (PMSI) has been added to this claims database, which includes admission and discharge diagnoses, from which serious AEs requiring hospitalisation can be identified.

The first available data in EGB dates from 2003 and each included subject will be followed for 20 years.

9.5 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.

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 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.

Statistical analysis will be performed after database lock 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.

9.8 QUALITY CONTROL

The Department of Pharmacology have a quality system for all its activities, especially programming, database management, statistical analysis and report.

In order to avoid programing error for the main evaluation criterion, two statisticians will do independently the programing 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 1/97 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 APSECTS

NA.

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

This project is a database analysis using anonymous individual information. All events will be reported in the report of the study.

12 PLAN FOR DISSEMINATING AND COMMUNATING STUDY RESULTS

The interim and final study reports will be sent to the regulatory authorities at year 1 , year 2 and year 3 post-launch..

A contractual arrangement preserving the independent publication of the data by the investigator will be provided with the final version of the protocol. 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

1. P Malfertheiner, F Megraud, C O'Morain, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut 2007 56: 772-781

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