Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

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

Summary of the consolidated final study reports
Cohort 3 – one-year follow-up
Cohort 5 – one-month follow-up

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Bordeaux PharmacoEpi
Plateforme de recherche en pharmaco-épidémiologie
Service de Pharmacologie médicale, CIC Bordeaux CIC1401
INSERM - Université de BORDEAUX - CHU de Bordeaux - Adera
Bâtiment Le Tondu - case 41
146 rue Léo Saignat - 33076 Bordeaux Cedex

SPONSOR REPRESENTATIVES	
• **Aptalis Pharma SAS US** An affiliate of Actavis, Inc. **Allergan Pharmaceuticals International Limited**	Harborside Financial Center, Plaza V Jersey City, NJ 07311, US Tour Manhattan 5/6 Place de l'Iris 92400 Courbevoie FRANCE Clonshaugh Industrial Estate Coolock Dublin 17 Ireland
• Clinical Science Lead, Actavis, plc.	Robert H. Palmer, MD Bob.Palmer@allergan.com
• Executive Director, Epidemiology, Allergan, Inc.	Anita Verga anita.verga@allergan.com
• EEA Qualified Person for Pharmacovigilance Allergan, Inc.	Ilse Sjoholm Ilse.Sjoholm@allergan.com
• Statistical Science and Programming, Allergan, Inc.	Larry Xie, PhD larry.xie@allergan.com

COORDINATING CENTRE	
Bordeaux PharmacoEpi (BPE) Research Platform in Pharmacoepidemiology	Service de Pharmacologie médicale CIC Bordeaux CIC1401 INSERM - Université de BORDEAUX, CHU de Bordeaux - Adera 146 rue Léo Saignat - case 41 33076 Bordeaux Cedex – France http://www.pharmacoepi.eu
• Head of Bordeaux PharmacoEpi	Pr Nicholas Moore, MD, PhD nicholas.moore@u-bordeaux.fr
• Scientific project leader	Dr Patrick Blin, MD patrick.blin@u-bordeaux.fr
• Chief Operating Officer	Cécile Droz-Perroteau, PhD cecile.droz@u-bordeaux.fr
• Project Manager	Magali Rouyer magali.rouyer@u-bordeaux.fr
• Project Manager assistant	Estelle Guiard estelle.guiard@u-bordeaux.fr
• Chief Statistics & Data-Management	Régis Lassalle regis.lassalle@u-bordeaux.fr
• Statistician	Abdelilah Abouelfath abdelilah.abouelfath@u-bordeaux.fr
• Statistician	Marine Pénichon marine.penichon@u-bordeaux.fr

LIST OF ABBREVIATIONS

ANSM	*Agence Nationale de Sécurité du Médicament et des produits de santé* (French medicines agency)
EGB	*Echantillon Généraliste de Bénéficiaires* (1/97th representative sample of the national insurance database)
H. pylori	*Helicobacter pylori*
LTD	Long-Term Disease
MAH	Marketing Authorisation Holder
PMSI	*Programme de Médicalisation des Systèmes d'Information* (National hospital-discharge summaries database system)
PPI	Proton Pump Inhibitors
SmPC	Summary of Product Characteristics
STT	Specific tritherapy to eradicate *H. pylori*
UBT	Urea Breath Test

Rationale and background

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. This drug is indicated in combination with omeprazole, for the eradication of *Helicobacter pylori* and prevention of relapse of peptic ulcers in patients with active or a history of *H. pylori* associated ulcers. The ANSM has raised some concerns regarding the potential risk of bismuth encephalopathy with Pylera®, a bismuth-containing compound. The Marketing Authorization Holder (MAH) anticipates the potential risk of bismuth encephalopathy would be increased in the setting of overdose or chronic use of Pylera®. The main marker of such misuse would be repeat prescription or dispensation of Pylera®, with or without indication of an *H. pylori* diagnosis or eradication failure. To address the request by the ANSM for a Drug Utilization Study in France, the MAH of Pylera® has entrusted the Department of Pharmacology, University of Bordeaux, with the evaluation of the product usage pattern after launch in order to describe the usage patterns of this drug in a real-life setting.

Methods

The Drug Usage patternS of Pylera® in a real-life setting in France (DUS study) was a longitudinal and dynamic cohort study of patients having a first Pylera® dispensation with a one-year follow-up for main criteria and a two-year follow-up for the secondary criterion, using the EGB database, a representative sample of the national claims and hospitalisations database.

The evaluation criteria were 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,
- New prescription of specific tritherapy to eradicate *H. pylori* (STT): indicator or proxy to assess treatment failure and defined as a 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 last dispensation of Pylera®.

The study was planned to include all patients with a first prescription of Pylera® with successive data extractions from April 2013 to March 2015, each representing an increment of the number of patients included in the preceding cohort, as well as of the follow-up duration (between one-month and two-year follow-up). The data extraction process had to take into account a lag of 6 months for reimbursed claims to be uploaded, the availability once a year (in September-October) of hospital information for the previous year including most endoscopies, and about 6 months for analysis and report.

Consequently, each successive and incremental cohort has been described using information available at the time of data extraction. Taking into account the

submission date of the annual study reports to the ANSM, the inclusion period of each cohort was 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.

The analysis of criteria took into account the period for completion and validation of EGB and hospitalisations databases. The availability of data for each criteria are summarised in Table 1. This consolidated final report provides separate cross-sectional and repetitive descriptions for 2 cohorts (detailed into 2 separate reports).

The main results are from cohorts 3 and 5, (results of cohort 1 submitted in June 2016 for treatment of recurrent infection at two-year of follow-up):

- ***Cohort 1 – two-year follow-up: 86 patients*** *having initiated Pylera® from 01 April 2013 to 30 June 2013 with a two-year follow-up after date of Pylera® initiation + 10 days (theoretical treatment duration).*
- **Cohort 3 – one-year follow-up: 540 patients** having initiated Pylera® from 01 April 2013 to 30 April 2014 with a one-year follow-up after date of Pylera® initiation + 10 days (theoretical treatment duration). Less than a sixth of these patients are from Cohort 1. The attached report provides results for: i) Number of drug packs dispensed per patient and per year, ii) Misuse at index date, iii) Normal use at index date, iv) Treatment failure at one-year of follow-up.
- **Cohort 5 – one-month follow-up: 1194 patients** having initiated Pylera® from 01 April 2013 to 31 March 2015 with a one-month follow-up after date of Pylera® initiation + 10 days (theoretical treatment duration). This cohort was constituted with 45% of patients from Cohort 3. The attached report provides results for: i) Number of drug packs dispensed per patient and per year, ii) Misuse at index date, iii) Normal use at index date. The description of pregnant women is not presented due to incomplete data regarding a short follow-up.

Milestones for reports of each cohort are summarised in Table 1.

Table 1: Availability of data per cohort according to criteria evaluated in the DUS study for preliminary and final reports sent to the Health authorities (ANSM).

		Availability of data		
		Cohort 1	**Cohort 3**	**Cohort 5**
Inclusion period -	start end	01/Apr/2013 30/Jun/2013	01/Apr/2013 30/Apr/2014	01/Apr/2013 31/Mar/2015
Number of dispensed packs at index date		✓	✓	✓
Misuse (at index date)		✓	✓	✓
Pylera® dispensation		✓	✓	✓
UBT before[a]		✓	✓	✓
Endoscopy[a] before		✓	✓	✓
One-Month follow-up:				
Data extraction		03/Feb/2014	12/Jan/2015	20/Jan/2016
Report (preliminary)[b]		15/Apr/2014	29/Jun/2015	28/Jun/2016
Data extraction		-	-	13/Feb/2017
Report (consolidated)[c]		-	-	**May 2017**
Number of packs dispensed per year		✓	✓	
Treatment failure*		✓	✓	
New dispensation[d*]		✓	✓	
One-year follow-up:				
Data extraction		12/Feb/2015	20/Jan/2016	
Report (preliminary)[b]		Jun 2015	28/Jun/2016	
Data extraction		15/Feb/2016	13/Feb/2017	
Report (consolidated)[c]		28/Jun/2016	**May 2017**	
Treatment of recurrent infection**		✓		
New dispensation[d] **		✓		
Two-year follow-up:				
Data extraction		20/Jan/2016		
Report		28/Jun/2016		

[a] endoscopy or UBT corresponds to hospital information (hospitalisations database)
[b] preliminary report: results based on data without 2015 hospital information
[c] consolidated report: results based on data with 2015 hospital information
[d] new dispensation of Pylera® or other specific treatment for *H. Pylori*
* during the 12 months of follow-up after first dispensation of Pylera®
** during the 24 months of follow-up after first dispensation of Pylera®
✓ data available at the time of this report

Results

The main results presented here correspond to Cohort 3, including additional data from Cohort 5 relative to misuse criterion, and additional data from Cohort 1 relative to the treatment of recurrent infection.

The main prescribers of Pylera® were gastroenterologists or hospital physicians for all cohorts, but the proportion of general practitioners tended to increase over time. General characteristics of these 540 patients (see details in study report of Cohort 3) were the following: median age was 54 years, 44% were men, 30% had one or more long-term diseases (LTD). Most of the patients (82%) did not have a previous specific therapy for the eradication of *H. pylori* before the first Pylera® prescription (one-year history). Nine patients (2%) had a hepatic or renal impairment and one patient was a pregnant woman at the index date, which are contraindications as per the summary of product characteristics (SmPC) of Pylera®.

At index date, 93% of the patients had at least one concomitant dispensation of a proton pump inhibitor (PPI): two third with omeprazole (specified in the SmPC) and one third with another PPI (esomeprazole, pantoprazole, rabeprazole, or lanzoprazole). In accordance with SmPC, almost all patients (98%) were dispensed only one pack of Pylera® at index date (Table 2), and this result remains the same in cohort 5 (99%). About 9 patients out of 10 (91%) had UBT or endoscopy performed in the year previous to the first Pylera® dispensation in accordance with recommendations of the French Health Authorities (*Haute Autorité de Santé*) (1).

Finally, a misuse criterion has been observed for 11% of patients, mainly for absence of formal demonstration of *H. pylori* infection (9%), plus 2% with dispensation of more than one pack of Pylera®. Taking into account the serology in exams performed in addition to UBT and endoscopy, misuse criterion slightly decreased to 9%. These results remain the same in cohort 5.

Within the one-year follow-up period of Cohort 3, a new prescription of a tritherapy to eradicate *H. pylori* (STT), indicating treatment failure, was observed for 5% after the first Pylera® treatment. Taking into account the non-STT dispensation in addition to STT dispensation after first Pylera® treatment, treatment failure increased to 8% of patients. This treatment failure rate corresponds to the known lower value of the eradication failure rate (from 10% to 30%) in France (2). However, only 13% of patients had a check of *H. pylori* infection eradication within one month after Pylera® treatment, and 55% within three-month after Pylera® treatment.

The recurrence of infection at two-year follow-up was evaluated on few patients in the Cohort 1 (86 patients), and taking into account the non-STT dispensation in addition to STT dispensation after first Pylera® treatment, the recurrence of infection (see study report of Cohort 1, 28 June 2016) was 1% that is slightly below the mean annual reinfection rate, approximately 3% per patient-year (3).

Table 2: Normal use, misuse and treatment failure

	Cohort 3 n = 540
Normal use, %	89.1
95% CI [a]	[86.4;91.7]
Misuse, %	10.9
95% CI [a]	[8.3;13.6]
Normal use (taking into account serology), %	90.6
95% CI [a]	[88.1;93.0]
Misuse (taking into account serology), %	9.4
95% CI [a]	[7.0;11.9]
New dispensation of STT in the year post-Pylera® treatment (treatment failure), %	5.0
95% CI [a]	[3.2;6.8]
New dispensation of STT+non-STT in the year post-Pylera® treatment (treatment failure), %	8.3
95% CI [a]	[6.0;10.7]

[a] Clopper-Pearson Binomial exact 95% CI

In conclusion, Pylera® use in a real-life setting generally conformed to the SmPC with only one dispensed pack for almost all patients. This alleviates the main concern of a risk of bismuth intoxication or overdose. In accordance with the SmPC, Pylera® was prescribed for the majority of patients in combination with a PPI, even though this latter was different from omeprazole for one third of cases, that should not really be considered outside the SmPC, in particular for those already treated by another PPI at the time of the prescription of Pylera®. On the other hand, the exam practices in terms of diagnosis of *H. pylori* infection, and notably the check of eradication after specific treatment were not consistent with recommendations of French health authority. A new dispensation of a specific treatment was done for 8% of patients after Pylera® treatment, an indicator of treatment failure that is close to the finding in the literature for the eradication failure rate of *H. pylori* infection (from 10% to 30%) in France.

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