Pharmacologie médicale

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A safety and pharmacokinetic study in real-life practice for Pylera® in France: the SAPHARY Study

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Abstract

Background: Pylera®, a capsule-based therapy with bismuth, metronidazole, and tetracycline, is indicated in eradication of Helicobacter pylori (*H. pylori*). Due to the history of bismuth encephalopathy risk, the French Health Authority has requested to conduct a post-marketing program in France to observe potential changes in bismuth concentrations.
Objectives: To verify the absence of bismuth accumulation in patients prescribed Pylera® in a real-life setting.
Methods: Minimal invasive observational study of patients treated with Pylera® for *H. pylori* infection, included and followed by gastroenterologists (GE) and general practitioners (GP) with 3 visits: at inclusion, at end of treatment (EOT) i.e. 10 days, and at 28 days after the EOT. A blood sample was obtained before the 1st Pylera® intake and 24h after the last Pylera® intake for a bismuth dosage by a centralized referral laboratory, and a 3rd sample in case of whole blood bismuth concentration >50 µg/L at 2nd sample.
Results: Among 202 patients included from 13 Mar 2014 to 2 Dec 2015 by 34 physicians (80% GE and 20% GP), 190 took at least one dose of Pylera® (Safety population) and 2 required blood samples were obtained from 167 (Per protocol population). Among Safety population, 46% were men and median age was 54 years. The Pylera® duration treatment was 10 days for 85% of patients. These characteristics were close to those of Per protocol population. Among these latter, the median bismuth concentration at the EOT was 15.4 µg/L (95%CI: [15.6; 18.3]). Two patients had a concentration >50 µg/L: 56.0 µg/L for a 83 years old woman with low weight (45 kg) associated with non-serious memory impairment during treatment, reversible after treatment discontinuation, and 50.9 µg/L for a 82 years old man without neurological AE. For Safety population, neurological AEs occurred for 20% of patients during treatment period, all non-serious, and 95% as related to Pylera® by investigators. Non-neurological AEs were observed for 25% of patients, mainly digestive disorders (19%), all non-serious, and 88% as related to Pylera®. No serious AE were reported during the study period. The eradication of *H. pylori* infection was confirmed in 71% of cases, treatment failure in 5%, while 24% were undetermined due to missing data for diagnostic test.
Conclusions: The SAPHARY study shows few cases (2 patients) of bismuth concentration >50 µg/L without severe neurology AE with Pylera®. The effectiveness and safety profiles in a real-life setting seem to be close to those found in the literature.

Conflict of Interest Statement

This study was performed at the request of the French Health Authorities, supported by an unconditional grant from successively Axcan, Forest, Actavis, Aptalis, Allergan, and supervised by an independent expert Scientific Committee. It was designed, conducted, and analyzed independently by the Bordeaux PharmacoEpi Platform, CIC Bordeaux CIC1401 of the Bordeaux University. This study was registered with the European Medicine agency's EUPAS registry (www.encepp.eu), under study number EUPAS3142, and carries the "ENCePP Study" seal.

Background

- **Pylera®:** capsule-based therapy with bismuth, metronidazole, and tetracycline, indicated in eradication of Helicobacter pylori (*H. pylori*).
- **MAA** in France 10 April 2013.
- **Bismuth (Bi) withdrawn from French market** in 1975 for an **encephalopathy risk**.
- Due to this potential risk, the French Health Authority has requested to conduct a post-marketing program in France **to observe potential changes in bismuth concentrations.**

Objectives

- **Principal objective:** To verify the absence of bismuth accumulation in patients prescribed Pylera® in a real-life setting.
- **Secondary objective:** To evaluate treatment effectiveness and safety data.

Method

- **Study design:** Minimal invasive observational study of patients treated with Pylera® for *H. pylori* infection
  - ✓ Patients included and followed by gastroenterologists (GE) and general practitioners (GP) in France.
  - ✓ Signed Informed Consent Form.
  - ✓ 3 visits: Inclusion (Day 0), End of treatment (Day10), End of study (28 days after end of treatment).
  - ✓ 2 blood samples: before 1st Pylera® intake, and 24h after last Pylera® intake (Day 11).
  - ✓ Bismuth dosage centralized in the referral laboratory of Angers University Hospital.
  - ✓ Toxicity threshold of 50 µg/L in whole blood; 3rd optional blood sample if at 2nd sample whole blood [Bi] was > 50 µg/L.
  - ✓ Safety population: patients included and analyzable with at least one Pylera® taken.
  - ✓ Per Protocol population: patients of Safety population who provided the 2 blood samples for bismuth dosage.

Results

- **Study population**

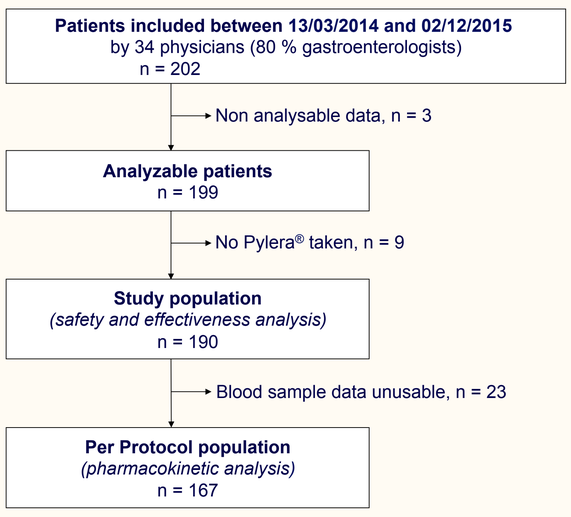

Figure 2: Identification of study population

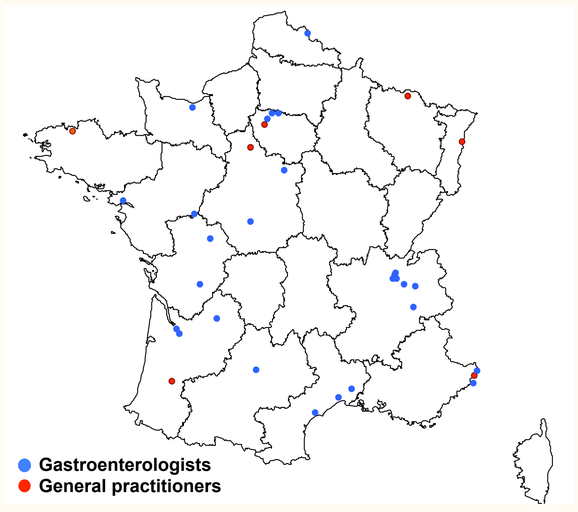

Figure 3: Repartition of participating physicians

- **Patients characteristics and conditions of Pylera® use**
  - ✓ Patients characteristics and conditions use of Pylera® were close in the two populations (Safety and Per protocol)

Table 1: Patients characteristics and duration of Pylera®

	Safety population n = 190	Per Protocol population n = 167
Men, n (%)	88 (46.3)	73 (43.7)
Median age, years (± standard deviation)	53.4 (14.3)	54.2 (14.1)
Previous treatments prescribed for the eradication of *H. pylori*, n (%)	44 (23.2)	40 (24.0)
≥ one PPI prescribed or ongoing at inclusion, n (%)	190 (100.0)	167 (100.0)
PPI prescribed or ongoing at inclusion*, n (%)		
Oméprazole	132 (69,5)	117 (70,1)
Esoméprazole	34 (17,9)	29 (17,4)
Pantoprazole	13 (6,8)	10 (6,0)
Lansoprazole	6 (3,2)	6 (3,6)
Rabéprazole	6 (3,2)	6 (3,6)
Duration of Pylera® treatment (days)		
< 10	8 (4.2)	2 (1.2)
10	161 (84.7)	146 (87.4)
>10	21 (11.1)	19 (11.4)

** among patients with PPi(s) prescribed or ongoing at inclusion*

- **Bismuth concentration [Bi] whole blood**
  - ✓ 2 patients (1.2%) had a bismuth concentration in whole blood > 50 µg/L. Their characteristics are described in Table 3.

Table 2: Concentrations of whole blood bismuth before and after Pylera® treatment

	Per Protocol population n = 167	
	Before treatment	After treatment
Whole blood [Bi] in categories in µg/L, n (%)		
Missing data	1 (0.6)	3 (1.8)
Whole blood [Bi] < 1.2 µg/L	166 (99.4)	2 (1.2)
Whole blood [Bi] [1.2 µg/L ; 50.0 µg/L]		160 (95.8)
Whole blood [Bi] > 50.0 µg/L		**2 (1.2)**
Whole blood [Bi] in µg/L		
Size (missing data)		163 (4)
Median		15.4
[p25% ; p75%]		[11.2 ; 21.7]
[Min ; Max]		[0.0 ; 56.0]
[CI 95%]		[15.6 ; 18.3]

- **Patients characteristics with bismuth concentration > 50 µg/L**
  - ✓ One of the two patients presented a neurological adverse event (memory impairment) considered as non-serious by investigator.

Table 3: Patients characteristics with whole blood bismuth concentration > 50 µg/L

	Patient 1	Patient 2
Clinical data		
Gender	Male	Female
Age in years	82	83
Weight in kg	62	45
Body Mass Index in kg/m²	< 25	< 25
Previous treatments for *H. pylori* eradication	none	1st line
Neurological adverse event during the complete study period	none	Memory impairement*
Pharmacokinetic data		
Whole blood [Bi] after Pylera® intake (2nd blood sample) in µg/L	50.9	56.0
Whole blood [Bi] at 3rd blood sample in µg/L	37.7	25.9
Estimated time required to go down to 50 µg/L in hours	9.9	50.0
Interval between 2nd et 3rd blood sample in hour	167.0	340.0

** from 2nd to 10th day of Pylera® treatment*

- **Safety and effectiveness**
  - ✓ Neurological adverse events (AE) occurred for 20% of patients, 95% as related to Pylera®, and non neurological AE occurred for 24.7% of patients, 88% as related to Pylera®. All AE were not serious (Table 4).

Table 4: Occurrence of AE during the study period

	Safety population n = 190
Neurological AE, n (%)	38 (20.0)
Type of neurological AE (frequency > 2%), n (%)	
Headache	11 (5.8)
Sleep disorders	7 (3.7)
Dysgeusia	5 (2.6)
Non neurological AE, n (%)	47 (24.7)
Type of non neurological AE (frequency > 2%), n (%)	
Digestive disorders	33 (17.4)
Asthenia	13 (6.8)
Infection and infestation	4 (2.1)

  - ✓ *H. pylori* eradication was confirmed for 71% of patients (Table 5).

Table 5: Response to Pylera® treatment

	Safety population n = 190
At least one positive *H. pylori* diagnostic test before Pylera® treatment, n (%)	
Not done	5 (2.6)
Yes	185 (97.4)
Eradication of *H. pylori*	
Undetermined*	46 (24.2)
No	10 (5.3)
Yes	134 (70.5)
[CI 95%]	[64.0 ; 77.0]

** "Undetermined" if no test was performed, or if all tests were performed less than 28 days after the end of Pylera® treatment, or if only a serology test with positive result was performed, or all test results were missing.*

Conclusion

- **Bismuth accumulation > 50 µg/L:** about 1% of patients, without serious neurological adverse event, neither encephalopathy symptom,
- **Safety:** profile in real-life setting close to Summary of Product Characteristics
  - ✓ 20% of patient with non-serious neurological AE
  - ✓ 24.7% of patients with non-serious non neurological AE, and mainly digestive,
- **Effectiveness:** *H. pylori* eradication rate of at least 71%, close to that found in the literature.