Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

A Safety and Pharmacokinetic study in Real-life practice of Pylera® in France: The SAPHARY Study

Abstract of Final Study Report

V1.0 – 25 October 2016

CENTRE COORDINATEUR
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

Title: A Safety and Pharmacokinetic study in Real-life practice of Pylera® in France: The SAPHARY Study

Keywords: bismuth, neurological adverse event

Rationale and background:
The bacterium *Helicobacter pylori* (*H. pylori*) has been known for nearly 25 years to be responsible for gastritis and peptic ulceration, and to play an important role in the development of gastric carcinoma and mucosa associated lymphoid tissue (MALT) lymphoma. Aptalis Pharma US developed Pylera®, an innovative capsule-based therapy containing bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride, to be administered as 3 capsules 4 times a day for 10 days with omeprazole, a proton pump inhibitor (PPI). Pylera® has been marketed in France since 10 April 2013. The French Regulatory Authority, *Agence Nationale de Sécurité du Médicament et des produits de santé* (ANSM), has raised some concerns regarding the potential risk of bismuth encephalopathy with Pylera®, a bismuth-containing compound. These concerns were related to cases of encephalopathy associated with oral bismuth salts which occurred in the 1970's. Such toxicities have historically been associated with prolonged daily intake of large quantities of bismuth. As part of the Pylera® Marketing Authorisation Application, a post-marketing program to be conducted in France was requested to observe potential accumulation of bismuth arising from real-life use of Pylera® in the general population, including poor compliance, misuse, or the concomitant use of other medications. The SAPHARY study was designed to address this request.

This final report submission was planned with the ANSM for October 2016.

Research question and objectives:
Primary objective: to verify the absence of accumulation of bismuth in patients prescribed Pylera® in a real-life setting.
Secondary objectives: to evaluate treatment effectiveness and safety data.

Study design:
French multicenter, minimally invasive observational study of patients prescribed Pylera® and followed for 6 weeks, with a blood sample at Day 0 and Day 11 for bismuth whole blood and plasma assay and a third test in case of total bismuth concentration in whole blood > 50 µg/L at Day 11.

Setting:
The study was conducted in a real world setting by planning a sample of 100 General practitioners (GP) and 40 Gastroenterologists (GE).

Subjects and study size, including dropouts:
200 eligible patients, having been prescribed Pylera®, were planned to be enrolled in the study.

Variables and data sources:
Medical data were collected by the investigator physician using a paper Case Report Form (CRF) and bismuth whole blood and plasma assays were performed by a central University Hospital laboratory. The main outcome of the study was bismuth accumulation in whole blood, defined as a greater than 50 µg/L difference of bismuth concentration between End of Treatment and Day 0. Other outcomes were plasma bismuth concentration, interval between Pylera® intake and blood samples, safety

profile assessed in terms of overall AEs, vital signs, and concomitant medication used over the complete study period, and effectiveness was evaluated in terms of eradication of *H. pylori* as regards to the results of diagnostic tests before and after Pylera® treatment.

Results:
For this final data analysis, 202 patients were included by 34 physicians (80% gastroenterologists and 20% general practitioner) between 13 March 2014 and 2 December 2015. Inconsistencies in data were identified for one centre with 3 patients that were excluded from the analysed population (n=199). Among them, 190 patients took at least one dose of Pylera® and corresponded to the Safety population. Among this Safety population (n=190), 46% were men with a median age of 54 years, 73% had a medical and surgery history, and 57% an ongoing comorbidity. A previous *H. pylori* eradication treatment had been prescribed for 23% of patients. The duration of Pylera® treatment was between 10 and 12 days for most of the patients (95%) but 9 patients prematurely discontinued the treatment: 5 patients for AE (associated with personal decision for 3 of them), one patient for personal decision, and 3 patients for other reasons, difficulty swallowing capsules associated with personal decision (1), forgotten intake (1), and investigator decision after a vaso-vagal episode (1). All patients had at least one PPI (70% omeprazole), prescribed or ongoing at inclusion. Among the Safety population, 167 patients provided first and second blood samples for plasma and/or whole blood pharmacokinetic data, and performed their second blood sample within 48 hours after the last intake of Pylera®. They corresponded to the Per Protocol population. Their characteristics were close to the Safety population. The main outcome was evaluated in this Per Protocol population (n=167). Before first dose of Pylera®, the bismuth concentration was undetectable in whole blood (<1.2 μg/L) or considered as zero with a value between 0.5 μg/L and 1.00 μg/L in plasma for all patients. The median whole blood bismuth concentration at the end of treatment was 15.4 μg/L, with a mean of 17.0 μg/L (95%CI: [15.6; 18.3]), including two patients with a concentration > 50 μg/L: 50.9 μg/L for one without neurological AE and 56.0 μg/L for the other with memory impairment during Pylera® intake (from Day 2 to the end of treatment); this neurological event was not classified as serious and was reversible after Pylera® treatment discontinuation.

Moreover, among those excluded from the Per Protocol population, because of a second blood sample obtained more than 48 hours after the last intake of Pylera®, two patients had a high bismuth concentration in whole blood, with a calculated minimum bismuth concentration greater than 50 μg/L (62.5 μg/L and 65.2 μg/L), estimated from a pharmacokinetic model, and one presented abdominal distension and faeces discoloured considered as non-serious by the investigator. No neurological event was reported for these 2 patients.

Safety was evaluated in the Safety population (n=190). At least one AE was observed for 35% of patients and there were no serious events over the complete study period. The AEs occurred during the treatment period for 97% of patients concerned. Neurological AEs occurred for 20% of patients during the complete study period, and 95% were reported as related to Pylera® by investigators, including the case of memory impairment described above. Non-neurological AEs were observed for 25% of patients during the complete study period. These non-neurological AEs were considered as related to Pylera® treatment in 88% of cases. The most frequent non-neurological AEs were digestive disorders (19%), asthenia (7%), and infections or infestations (3%).

Taking into account a positive *H. pylori* diagnostic test before Pylera® prescription and a negative test at the end of the study (excluding the serological test), the eradication of *H. pylori* infection was confirmed in 71% of patients of the Safety population, treatment failure was observed for 5% of patients, while 24% were undetermined (missing information for initial or final diagnostic test). Consequently, if these latter were considered as treatment failure, this proportion could increase up-to 29%.

Discussion:

For the 167 patients who had a second whole blood assay, two presented a concentration of bismuth at the end of treatment higher than the 50 μg/L threshold, defined as the difference of whole blood bismuth concentration greater than 50 μg/L, including one with a non-serious neurological symptom (memory impairment). One out of 5 patients reported a neurological AE, related by investigators to Pylera® treatment for 95% them (i.e. 35 neurological AEs), all non-serious and none classified as encephalopathy. The safety profile of Pylera® in the SAPHARY study is not different from the description of adverse events in the SmPC, notably for neurological adverse events and digestive disorders.

The SmPC indicates a prescription of Pylera® combined with omeprazole such as performed in clinical trials, but in the SAPHARY study, the combination with other PPI was found related to the usual clinical practice of physicians. Pylera® was used in the study as a second-or-more line therapy for 1 in 4 patients. This could be explained by a channelling of the product to patients with previous treatment failure, in a country with a high level of resistance to clarithromycin. The treatment failure concerned 5% of patients and taking into account the undetermined response to treatment as treatment failure, this rate could increase up-to 29%, close to the known value of the eradication failure rate of *H. pylori* in France.

The SAPHARY study shows few cases (2 cases in the Per protocol population) of bismuth concentration greater than 50 μg/L with Pylera® (a combination of bismuth subcitrate potassium, metronidazole, and tetracycline) without severe neurology AEs or encephalopathy symptoms. No risk factor for increased bismuth concentration in the blood has been identified. The effectiveness and the safety profiles in real-life practice seem to be close to those found in the literature.