HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

3 October 2012

The draft Opinion adopted by the Transparency Committee on 18 July 2012 was examined at a hearing on 3 October 2012.

PYLERA 140 mg/125 mg/125 mg, capsule
HDPE bottle with child-proof closure containing 120 capsules (CIP code: 218 042-0)

Applicant: APTALIS PHARMA S.A.S.

Bismuth subcitrate potassium
Metronidazole
Tetracycline hydrochloride

ATC code: A02BD08 (Combinations for eradication of *Helicobacter pylori*)

List I

Date of Marketing Authorisation (decentralised procedure, rapporteur Member State Germany, France one of the recipient countries): 16 January 2012

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Combination of three active ingredients:

- Bismuth subcitrate potassium 140 mg
- Metronidazole 125 mg
- Tetracycline hydrochloride 125 mg

1.2. Indication

“In combination with omeprazole, PYLERA is indicated 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.”

1.3. Dosage

“Each dose of PYLERA includes 3 identical hard capsules. Each dose should be taken 4 times a day, 3 capsules after breakfast, 3 capsules after lunch, 3 capsules after the evening meal, and 3 capsules at bedtime (preferably with a snack) for a total of 12 capsules per day over a period of 10 days.
One omeprazole 20 mg capsule/tablet should be taken twice a day, at the same time as the breakfast and evening meal doses of PYLERA, for the full 10 days of treatment.

Table 1: Daily dosing schedule for PYLERA

Time of dose	Number of capsules of PYLERA	Number of capsules/tablets of omeprazole
After breakfast	3	1
After lunch	3	0
After evening meal	3	1
At bedtime (preferably with a snack)	3	0

[…]

Patients with hepatic or renal impairment
PYLERA is contraindicated in patients with renal or hepatic impairment. The safety and effectiveness of PYLERA in hepatic or renal impairment has not been evaluated.

Geriatric patients
Experience in geriatric patients is limited. In general, the greater prevalence of decreased hepatic, renal or cardiac function, as well as the presence of concomitant diseases and multiple concomitant therapies should be considered when prescribing PYLERA in this patient population.

Paediatric population
PYLERA is contraindicated in patients less than 12 years of age and is not recommended in children 12 to 18 years of age.

Method of administration: For oral use. […]

1.4. Contraindications

“”PYLERA is contraindicated in: pregnant or breast-feeding women, children (up to 12 years of age), patients with renal or hepatic impairment, and in patients with hypersensitivity to bismuth subcitrate potassium, metronidazole or other nitroimidazole derivatives, tetracyclines or to any of the excipients.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

A	Alimentary tract and metabolism
A02	Drugs for acid related disorders
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease
A02BD	Combinations for eradication of *Helicobacter pylori*
A02BD08	Bismuth subcitrate potassium, tetracycline and metronidazole

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

There are no medicines strictly comparable with PYLERA.

2.2.2. Not strictly comparator medicines

The following free combinations fall within the same pharmacotherapeutic category (A02BD: Combinations for eradication of *Helicobacter pylori*):

- omeprazole, amoxicillin and metronidazole,
- lansoprazole, tetracycline[1] and metronidazole
- lansoprazole, amoxicillin and metronidazole,
- pantoprazole, amoxicillin and clarithromycin,
- omeprazole, amoxicillin and clarithromycin,
- esomeprazole, amoxicillin and clarithromycin,
- lansoprazole, amoxicillin and clarithromycin.

[1] Tetracycline is no longer on the market in France

3 ANALYSIS OF AVAILABLE DATA

The dossier comprises:

- Three phase III studies evaluating the efficacy and safety of PYLERA in combination with omeprazole:
  - two non-inferiority studies versus the amoxicillin/clarithromycin combination
    - study HPST99-CUS01, carried out in the USA between 1999 and 2000.[2]
    - study PYLHp07-01, carried out in Europe between 2008 and 2009.[3]
  - a non-comparative study (study HPST99-INT01), carried out in Europe and North America in 2000.[4]
- A comparative follow-up cohort study evaluating the risk of neurotoxicity due to the bismuth in PYLERA, the risk of the development of *C. difficile*, and the general safety profile.
- AFSSAPS Public Evaluation Report (RAPPE).

3.1. Context of medical need (extract from the RAPPE)[5]

"Currently, the therapeutic management of HP eradication in France is based on a combination of two antibiotics and a proton-pump inhibitor (PPI), in the form of one morning dose and one evening dose of each proprietary medicinal product. The recommended first-line treatment is: clarithromycin + amoxicillin + proton-pump inhibitor (PPI), a treatment that currently only has about a 70% success rate (failure due to resistance of HP to clarithromycin, the percentage resistance is increasing to about 20%).
Thus, PYLERA meets a known medical need, in view of the development of antibiotic resistance and poor compliance with the treatments currently available for HP infections, which has been identified as a source of failure. For this reason, PYLERA has already been the subject of temporary usage authorisations in France. In addition, PYLERA conforms to the European guidelines, since the Maastricht III Conference on the management of *H. pylori* infections (2006) mentions the interest in quadruple therapy including bismuth as a therapeutic option.
The combination of active substances in PYLERA is justified on a microbiological basis: few reports of *H. pylori* resistant to tetracycline (*this antibiotic has already been identified as a potential candidate in the treatment strategy for H. pylori),* metronidazole frequently induces resistance in *H. pylori*, but this is less significant than resistance to clarithromycin (*antibiotic used in first-line treatment*), action of bismuth itself on *H. pylori*.
Bismuth was withdrawn from the market in France in 1975 because of its neurological toxicity, particularly the risk of encephalopathy. Bismuth was used for the treatment of gastrointestinal complaints such as irritable bowel syndrome at large doses and for prolonged periods. However, in contrast to those bismuth salts, PYLERA contains a small quantity of bismuth (PYLERA 1680 mg/day *versus* 5 to 20 g/day), in the form of a different salt from those implicated in the cases of encephalopathy (PYLERA: bismuth subcitrate potassium *versus* insoluble salts), is prescribed for a shorter treatment period (PYLERA: 10 days versus 1 month to 30 years), and there is reassuring experience relating to the risk profile of bismuth (safety data from the United States, where PYLERA has been on the

[2] **Laine L, Hunt R, El-Zimaity H et al.** Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of Helicobacter pylori in duodenal ulcer patients: a prospective, randomized, multicenter, North American trial. **Am J Gastroenterol 2003; 98: 562-7.**
[3] **M**alfertheiner P, Bazzoli F, Delchier JC et al. Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. Lancet 2011; 377: 905-913.
[4] O'Morain C, Borody T, Farley A et al. Efficacy and safety of single-triple capsules of bismuth biskalcitrate, metronidazole and tetracycline, given with omeprazole, for the eradication of Helicobacter pylori: an international multicentre study. Aliment Pharamacol 2003; 17: 415-20.
[5] Public Evaluation Report, PYLERA 140mg/125mg/125mg, capsule, AFSSAPS.

market since May 2007, use of colloidal bismuth, which is comparable with bismuth subcitrate potassium and on the market in some European countries)."

3.2. Efficacy

The efficacy data are taken from the non-inferiority studies and the non-comparative study.

3.2.1. Studies HPST 99-CUS01 and PYLHp01-01

- Methods

The principal characteristics of the two non-inferiority studies (HPST99-CUS01 and PYLHp07-01), which were of similar methodology, are described in Table 2.

Table 2: Characteristics of the studies HPST99-CUS01 and PYLHp07-01

	HPST99-CUS01	**PYLHp07-01**
Objective	Randomised, open, non-inferiority study (delta threshold = 10%) the objective of which was to evaluate the percentage eradication of *H. pylori* (*HP*) after 10 days of treatment with PYLERA versus amoxicillin + clarithromycin (AC) for 10 days. Both treatments were combined with omeprazole.	Randomised, open, non-inferiority study (delta threshold = 10%) the objective of which was to evaluate the percentage eradication of *HP* by PYLERA for 10 days versus AC for 7 days. Both treatments were combined with omeprazole.
	The implementation of the studies as open studies was justified by: - the difference in the number of medicinal products per dose (2 medicinal products for quadruple therapy, 3 tablets for triple therapy), - the fact that specific adverse effects are expected with PYLERA – blackening of the tongue and metallic taste – which make it easily recognizable. The results were evaluated blind by an independent central laboratory.	
Inclusion criteria	Men or women 18 to 75 years of age.	Men or women (not pregnant and not breastfeeding and using contraception if of childbearing age) over 18 years of age.
	Positive for *HP* in both the urea breath test (UBT) and histology or UBT and culture	Positive for *HP* in both the UBT and rapid urease test (RUT) and at least one of two biopsies positive and a positive culture including the PCR
	Presence or history (in the last 5 years) of a duodenal ulcer of at least 3 mm documented by endoscopy or radiology	Presence of gastrointestinal symptoms
Treatments	PYLERA group: 3 PYLERA capsules 4 times a day for 10 days	
	AC group: amoxicillin 500 mg, 2 capsules twice daily and clarithromycin 500 mg, 1 tablet twice daily for **10 days**.	AC group: amoxicillin 500 mg, 2 capsules twice daily and clarithromycin 500 mg, 1 tablet twice daily for **7 days.**
	All the patients were also given 20 mg of omeprazole twice daily.	
Primary efficacy endpoint	Percentage eradication of *HP* based on negative UBT results in weeks 6 and 10. The non-inferiority of PYLERA with respect to AC was established if the lower limit of the 95% CI of the difference between the percentage eradications was greater than -10% (*per-protocol* analysis).	
		In the event of the demonstration of non-inferiority, a superiority analysis was planned. The superiority was established if the lower limit of the CI of the difference was greater than 0 (intention-to-treat analysis).
Secondary endpoints	Percentage eradication of *H. pylori* as a function of metronidazole and clarithromycin resistance Percentage eradication of *H. pylori* as a function of a history of ulcer or an active ulcer Resistance induced by the treatments Safety	

- Results

Study HPST99-CUS01

Study population

Of the 299 patients randomised, 147 were assigned to the PYLERA group and 152 to the AC group.

The mean age was 46.6 years versus 47.2 years. In the PYLERA group, 62.6% (92/147) had a history of duodenal ulcer or an active duodenal ulcer and 13.6% (20/147) had a history of gastric ulcer or an active gastric ulcer. In the AC group, this was 55.3% (84/152) and 13.2% (20/152).

In the modified intention-to-treat population (mITT),[6] 12.2% (14/114) of patients in the AC group were resistant to clarithromycin and 40.8% (51/125) of patients in the PYLERA group were resistant to metronidazole.

Results

In the *per-protocol* population[7] (PP), the percentage eradication of *HP* was 92.5% (111/120) in the PYLERA group versus 87.1% (108/124) in the AC group, which is a difference of 5.4%; 95% CI [-2.1%; 13.0%]. The lower limit of the confidence interval for the difference between the groups was -2.1%, which established the non-inferiority of PYLERA treatment with respect to AC treatment. These results were confirmed in the mITT population, with percentages eradication for *HP* of 87.7% (121/138) in the PYLERA group and 83.2% (114/137) in the AC group, difference 4.5%; 95% CI [-3.9%; 12.8%].

In relation to the secondary criteria, there was no significant difference between the percentages of eradication of *H. pylori* in the PYLERA group as a function of the presence or absence of metronidazole resistance. A significant difference was observed for the AC group as a function of clarithromycin resistance, with a percentage eradication of 93/101 (92.1%) among the patients with clarithromycin-sensitive *HP* versus 3/14 for clarithromycin-resistant *HP* (Table 3).

[6] mITT (modified intention-to-treat) population: patients selected and randomised in the study with a documented history of ulcer, positive for *HP* and without significant exclusion criteria.

[7] PP population: patients positive for *HP* at inclusion with a documented history of ulcer, without significant exclusion criteria, without major deviation from the protocol and with two available UBT control tests.

Table 3: Study HPST99-CUS01: Percentage eradication of *H. pylori* during the study

Population	mITT		PP	
Treatment*	PYLERA N = 138	AC N = 137	PYLERA N = 120	AC N = 124
Duration of treatment	10 days	10 days	10 days	10 days
Percentage eradication, n (%)	121 (87.7%)	114 (83.2%)	111 (92.5%)	108 (87.1%)
Difference [95% CI] p	4.5% [-3.9%; 12.8%] 0.293		5.4% [-2.1%; 13.0%] 0.164	
Percentage eradication as a function of sensitivity at inclusion				
Metronidazole resistant	41/51 (80.4%)	ND	38/44 (86.4%)	ND
Metronidazole sensitive	68/74 (91.9%)	ND	61/64 (95.3%)	ND
Clarithromycin resistant	ND	3/14	ND	3/13
Clarithromycin sensitive	ND	93/101 (92.1%)	ND	88/93 (94.6%)
Percentage eradication as a function of the age of the history of ulcer or presence of ulcer at inclusion				
Active ulcer	15/15	12/13	14/14	11/12
Duodenal ulcer less than 2 years ago	97/114 (85.1%)	96/116 (82.8%)	88/97(90.7%)	91/104(87.5%)
Duodenal ulcer 2-5 years ago	12/12	6/8	9/9	6/8

ND = Not determined
AC= amoxicillin + clarithromycin
* The two treatments (PYLERA versus AC) were combined with omeprazole.

Study PYLHp07-01

Study population

Of the 440 patients randomised, 218 were assigned to the PYLERA group and 222 to the AC group. 11.5% (25/218) of patients in the PYLERA group and 37.4% (83/222) in the AC groups discontinued treatment prematurely, the principal reason being a positive UBT in week 6.

The characteristics of patients in the two groups were comparable. The mean age was 48.5 years in the PYLERA group and 47.9 years in the AC group. The majority of patients included had non-ulcerative dyspepsias (85-90%).

In the intention-to-treat population[8] (ITT), 13.1% (29/222) of the patients in the AC group were resistant to clarithromycin and 22.2% (48/216) of the patients in the PYLERA group were resistant to metronidazole.

Results

In the *per-protocol* population[9], the percentage eradication of *HP* was 93.3% (166/178) in the PYLERA group versus 69.6% (112/161) in the AC group, i.e. a difference of 23.7% [15.5; 32.3%]. Because the lower limit of the confidence interval for the PYLERA-AC difference was >-10%, the non-inferiority of PYLERA treatment with respect to AC treatment has been established.

The analyses of the ITT population produced similar results, with a percentage eradication of 92.6% (174/188) in the PYLERA group versus 67.6% in the AC group, a difference of 25,0% [16.7-33.3%]. The lower limit of the 95% CI was > 0, suggesting that PYLERA is superior to AC (Table 4).

[8] ITT population: patients selected and randomised in the study.
[9] *Per-protocol* population: Patients from the ITT population who did not present a major protocol violation, did not discontinue treatment, did not take any banned treatment, compliance between 80 and 120%.

Table 4: Study PYLHp07 – primary endpoint: percentage eradication of HP (negative tests in weeks 6 and 10 (PP population))

Treatment*	PYLERA	AC	Difference [95% CI]	p superiority
PP population	166/178 (93.3%)	112/161 (69.6%)	23.7% [15.1-32.3%]	< 0.001
ITT population (observed cases)	174/188 (92.6%)	123/182 (67.6%)	25.0% [16.7-33.3%]	< 0.001
ITT population (missing data = failure)	174/218 (79.8%)	123/222 (55.4%)	24.4% [15.5-33.3%]	< 0.001

AC = amoxicillin + clarithromycin
* Both treatments (PYLERA versus AC) were combined with omeprazole.

The results for the secondary endpoints are presented in Table 5.

Table 5: Study PYLHp07 - Percentage eradication of HP (negative tests in weeks 6 and 10) as a function of antibiotic resistance or a history of ulcer or the presence of an active ulcer at inclusion

Treatment	PYLERA	AC
Sensitivity at inclusion		
Metronidazole resistant	38/42 (90.5%)	28/41 (68.3%)
Metronidazole sensitive	98/103 (95.1%)	64/90 (71.1%)
Clarithromycin resistant	30/33 (90.9%)	2/25
Clarithromycin sensitive	106/112 (94.6%)	90/106 (84.9%)
Sensitive to metronidazole and clarithromycin	125/133 (94.0%)	90/121 (74.4%)
History of ulcer or active ulcer at inclusion		
No history of ulcer or active ulcer	147/158 (93.0%)	95/141 (67.4%)
History of ulcer or active ulcer	18/19	15/18

AC = amoxicillin + clarithromycin
* Both treatments (PYLERA versus AC) were combined with omeprazole.

3.2.2. Study HPST99-INT01

The principal objective of this study was to evaluate, in patients with an *HP* infection, the percentage eradication of *HP* after 10 days of treatment with 3 capsules of PYLERA 4 times daily in combination with 20 mg of omeprazole twice daily.
Of the 187 patients included, 177 completed the treatment and 18 (10.2%) discontinued prematurely.
In the ITT population,[10] the percentage eradication of *HP* was 92.9% (158/170).
There was no difference between the percentage eradication as a function of the presence or absence of metronidazole resistance at inclusion (93% versus 95.3%, mITT population). Equally, the percentage eradication was similar (> 90%, ITT population) irrespective of whether a gastric or duodenal ulcer or of non-ulcerative dyspepsia was present at inclusion.

3.3. Safety

Safety data came from:

- phase III clinical studies and a grouped analysis of these studies,
- French temporary usage authorisations for named persons,
- post-marketing experience from the USA,
- a pharmacoepidemiological study.

3.3.1. Safety data from the phase III clinical studies

- Study HPST99-CUS01

Of the 147 patients randomised in the PYLERA + omeprazole group, 86 (58.5%) had at least one adverse event, the majority of which were considered to be due to the treatment, versus 90/152 (59.2%) in the omeprazole + amoxicillin + clarithromycin (OAC) group.

[10] ITT population: Patients who received at least one dose of treatment, did not violate the inclusion/exclusion criteria and were positive for HP according to the UBT and according to at least one of the culture test and the histological test.

The adverse events which were reported most often on PYLERA + omeprazole (> 8% and incidence higher than in the OAC group) were:

- gastrointestinal: abnormal stools: 15.6% (23/147) versus 4.6% (7/152),
- neurological: headaches: 8.2% (12/147) versus 7.2%(11/152).

Serious adverse events were reported in two patients in the PYLERA + omeprazole group, but were not considered to be due to the study treatment:

- respiratory failure secondary to pneumonia and leading to the death of the patient;
- gastrointestinal bleeding due to a duodenal ulcer and requiring hospitalisation of the patient.

- Study PYLHp07

Of the 216 patients randomised in the PYLERA + omeprazole group, 101 (46.8%) had at least one adverse event, just over half which were considered to be due to the treatment, versus 112/222 (50.5%) in the patients randomised in the OAC group.
The adverse events which were reported most often on PYLERA + omeprazole (> 8% and incidence higher than in the OAC group) were:

- gastrointestinal: upper abdominal pain: 8.3% (18/216) versus 7.2% (16/222);
- neurological: headaches: 8.3% (18/216) versus 3.2% (7/222).

Serious adverse events were reported in eight patients (four patients in each group), including one death in the OAC group (one case of suicide about two and a half months after the end of 10 days of treatment). One serious adverse event in the PYLERA + omeprazole group was considered to be possibly associated with the treatment (eczema and urticaria with skin desquamation 10 days after the discontinuation of treatment).

Three patients in the PYLERA + omeprazole group had at least one adverse event leading to the premature discontinuation of treatment, versus four patients in the OAC group; these events were mainly of a gastrointestinal nature.

Plasma concentrations of bismuth: Following treatment with PYLERA + omeprazole, the plasma concentrations of bismuth were increased in 21.5% of patients, with values between 4 µg/l (detection limit) and 20 µg/l. These values remained below the toxic threshold of 50 µg/l and had returned to normal (below the detection limit) in the majority of patients by week 10.

- Study HPST99-INT01

Of the 177 patients included, 129 (72.9%) had at least one non-serious adverse event, the majority of which were considered to be due to the treatment.
The adverse events reported most often (> 10%) were:

- gastrointestinal: abnormal stools: 35.6% (63/177); diarrhoea: 21.5% (28/177); nausea: 19,2% (34/177); abdominal pain 14.7% (26/177); and dyspepsia: 10.2% (18/177)
- neurological: dysgeusia: 22% (39/177) and headaches: 16.4% (29/177).

Four serious adverse events (anxiety, hyperventilation, nausea and abdominal pain) were observed in one patient, and resolved without sequel.
Six patients discontinued treatment because of an adverse event, mainly of a neurological (headaches, dizziness) or gastrointestinal (nausea, vomiting, diarrhoea, abnormal stools, stomatitis) nature. One patient had a generalized skin eruption.

- Combined analysis of the safety data from the 3 studies

Adverse events considered to be due to the treatment were reported in 237 patients (43.9%) in the PYLERA + omeprazole group and 127 patients (34.0%) in the OAC group.
The adverse events considered by the investigator to be due to the treatment that occurred in more than 1% of the patients are shown in Table 6.

This analysis shows an increase in transaminases (ALAT and ASAT) at the end of treatment in the PYLERA + omeprazole group of 14.1 IU/l and 8.3 IU/l versus 3 IU/l and 2.2 IU/l in the OAC group. A greater proportion of patients in the PYLERA + omeprazole group had increased ASAT and ALAT levels (23.9% and 16.6%) than in the OAC group (7.1% and 3.9%).

Table 6: Adverse events considered to be due to the treatment, frequency > 1/100

Adverse event	PYLERA + omeprazole N = 540 n (%)	OAC* N = 374 n (%)
Abnormal / discoloured stools (including black stools)	93 (17.2)	7 (1.9)
Nausea	57 (10.6)	15 (4.0)
Vomiting	14 (2.6)	2 (0.5)
Diarrhoea	56 (10.4)	41 (11.0)
Abdominal pain/upper abdominal pain	42 (7.8)	11 (3.2)
Dyspepsia	11 (2.0)	16 (4.3)
Dysgeusia (including metallic taste)	55 (10.2)	39 (10.4)
Dry mouth	10 (1.9)	2 (0.5)
Flatulence	8 (1.5)	7 (1.9)
Constipation	7 (1.3)	6 (1.6)
Anorexia/reduced appetite	6 (1.1)	1 (0.3)
Chromaturia	11 (2.0)	0
Headaches	39 (7.2)	9 (2.4)
Dizziness	26 (4.8)	5 (1.3)
Somnolence	16 (3.0)	0
Asthenia	23 (4.3)	4 (1.1)
Vaginal infection	7 (1.3)	3 (0.8)
Rash (including maculopapular rash, pruriginous rash)	12 (2.2)	4 (1.1)
Pruritus	3 (0.6)	4 (1.1)
Increased alanine aminotransferase	8 (1.5)	0

* omeprazole + amoxicillin + clarithromycin

3.3.2. TUA periodic reports

The first Temporary Usage Authorisation (TUA) for named patients for PYLERA was granted by Afssaps on 22 March 2010 (TUA number 399661).

In this case, the patients were treated with PYLERA for 10 days in salvage treatment for the eradication of *HP* in cases of repeated failure of eradication in multiresistant patients or patients with confirmed allergies to amoxicillin or clarithromycin.

Up to 31 March 2012, 280 boxes of 120 capsules had been delivered to hospitals within the framework of this TUA for named patients.
A summary of the pharmacovigilance data from France collected within the framework of the TUA covering the period from 22 March 2010 to 27 December 2010 was submitted to Afssaps on 28 February 2011.
Of the 54 patients treated with PYLERA + omeprazole, 15 (33%) had at least one adverse event. These 15 patients had 45 non-serious adverse events.
The most common adverse events were gastrointestinal complaints (diarrhoea, upper abdominal pain, nausea and vomiting), disorders of the nervous system (headaches and dysgeusia), as well as dizziness and asthenia.

3.3.3. Available post-marketing data from the United States

PYLERA has been on the market in the USA since 7 May 2007. Since that date, there have been no regulatory actions relating to safety.
From the time PYLERA was initially placed on the market up to 30 September 2010, 67 adverse effect reports relating to 176 adverse effects have been registered among the estimated 120,000 patients treated (8 serious and 168 non-serious).

Eight serious adverse effects were reported in five patients:

- one case of vomiting that resolved after the discontinuation of PYLERA,
- one case of blisters on the oral mucosa that resolved after the discontinuation of PYLERA,
- one case of oropharyngeal pain of unknown course,
- one case of severe abdominal pain with dizziness and nausea three days after the start of treatment with PYLERA that resulted in hospitalisation. The patient recovered under symptomatic treatment,
- on case of paraesthesia and peripheral neuropathy (non-serious) following the first dose of PYLERA. Ten days after the discontinuation of PYLERA, the patient was hospitalised for *Wegener's granulomatosis* and treated with corticoids and cytotoxic drugs. Leucopoenia subsequently appeared, probably provoked by the cytotoxic drugs. The illness was stabilised.

The adverse effects most frequently reported were similar to those observed in the course of the clinical studies.

3.3.4. Comparative follow-up cohort study

This was a historical cohort analysis on the basis of a database of an American healthcare reimbursement body collected within the framework of a post-marketing tolerability and safety study in patients treated with PYLERA or with PREVPAC (combination containing lansoprazole 30 mg, amoxicillin 500 mg and clarithromycin 500 mg) in the eradication of *HP*.

The objectives of this study were to evaluate the risk of the neurotoxicity[11] of the bismuth in PYLERA and the risk of the development of *C. difficile* infection compared with the incidence of this infection in patients treated with PREVPAC, as well as the general safety profiles of these two treatments.

Three cohorts of patients were created:
1) cohort of patients prescribed PREVPAC,
2) cohort of patients prescribed PYLERA,
3) “potential risk” cohort: patients prescribed PYLERA who had renal or hepatic impairment, neurological complaints or pregnant or breastfeeding women (corresponding to the contraindications to or precautions for use for PYLERA).

The study covered the period 1998 to 2008 for PREVPAC and 2007 to 2008 for PYLERA.
A total of 2538 patients given PYLERA, of whom 250 had a “potential risk”, and 54,732 given PREVPAC were included in the study.
There were no significant differences between the cohorts in terms of age or sex or in terms of the illnesses treated.

Three evaluation periods were defined:
(index date = date of prescription)

- 90 days before prescription (pre-index period),
- 40 days after prescription,

[11] The indicators of neurotoxicity due to bismuth chosen were diagnosis of central neuropathy or encephalopathy, peripheral neuropathy, or epileptic disorders according to the ICD-9-CM classification (International classification of diseases, ninth revision, clinical modification)

- 90 days after prescription, (post-index period).

The post-index period was the period during which tests for *Clostridium difficile* infection were carried out.

This study did not bring to light any major safety of use signals, particularly in terms of an increased risk of neurotoxicity or *C. difficile* infection.
Nevertheless, the results of this study should be interpreted with caution because of the major difference between the cohorts: 2538 patients for PYLERA and a study period of 2 years versus 54,732 patients for PREVPAC and a study period of 11 years.

3.3.5. Safety description according to the SPC

a. Summary of the safety profile

The adverse effects observed after concomitant administration of PYLERA and omeprazole in the course of controlled clinical studies were consistent with the known safety profiles of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride when they are administered separately. The safety profile of PYLERA observed in post-marketing is consistent with that established in the course of clinical studies.
The adverse effects most often observed (very common) with PYLERA were, in decreasing order of frequency: abnormal stools, diarrhoea, nausea and dysgeusia (including metallic taste).

b. Summary of adverse effects

The adverse effects were obtained from the data from the three phase III clinical studies (540 patients exposed to PYLERA) and post-marketing data (including spontaneous reports, statutory reports and literature data).
The frequencies of the adverse effects listed below are defined as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (≥ 1/10,000); not known (cannot be estimated from the available data).
Within each frequency group, the adverse effects are listed below in decreasing order of severity.

Table 7: Adverse effects

Very common (≥ 1/10)	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1000, < 1/100)**
	Vaginal infection	Candidiasis, buccal candidiasis, vaginal candidiasis
		Drug induced hypersensitivity
	Anorexia, reduced appetite	
		Anxiety, depression, insomnia
Dysgeusia (including metallic taste*)	Headaches, feelings of dizziness, somnolence	Hypoaesthesia, paraesthesia, amnesia, tremor
		Blurred vision
		Dizziness
Diarrhoea, nausea, abnormal stools (including black stools*)	Vomiting, abdominal pain (including upper abdominal pain), dyspepsia, constipation, dry mouth, flatulence	Oedema of the tongue, buccal ulceration, stomatitis, abdominal distension, eructations, discoloration of the tongue
	Increased alanine aminotransferase, increased aspartate aminotransferase	
	Rash (including maculopapular rash, pruriginous rash)	Urticaria, pruritus
	Chromaturia	
	Asthenic conditions**	Chest pain, chest discomfort

* Lowest level term (LLT); ** Highest level term (HLT)
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c. Description of some adverse effects

Black stools and discoloration of the tongue can occur with bismuth compounds, because of conversion into bismuth sulfide in the gastrointestinal system; stomatitis has been attributed to bismuth salts, but has also been reported during the use of metronidazole.

Like other antimicrobials, tetracycline can lead to the development of superinfections. The candidiases (buccal and vaginal) are probably due to tetracycline.

Somnolence, dysgeusia, headaches and chromaturia (dark coloration of the urine) are probably due to metronidazole.

Reversible and transitory increases in transaminases have been observed in clinical studies with PYLERA.

3.3.6. Risk management plan in France

Placing PYLERA on the market is conditional on a risk management plan (RMP) being put in place to monitor aspects relating to safety of use. The identified risks and actions envisaged by the RMP are summarised in Table 8.

Table 8: Identified risks and RMP actions

Safety risks	Planned actions
Identified major risks	
Candidiases and other superinfections	Routine pharmacovigilance
Peripheral neuropathies	Routine pharmacovigilance
Potential major risks	
Encephalopathies	Intensive monitoring programme Drug utilisation study relating to PYLERA Study of the safety and pharmacokinetics under practical conditions (SAPHARY)
Lack of efficacy	Targeted questionnaire Drug utilization study relating to PYLERA Study of the safety and pharmacokinetics under real-life conditions (SAPHARY) Investigation of the resistance of *H. pylori*
Use in special populations (with risk factors for peripheral neuropathies and encephalopathies)	Specific instructions to collect relevant information Drug utilisation study relating to PYLERA
Hepatotoxicity (including increases in liver enzymes)	Routine pharmacovigilance
Important missing information	
Pharmacokinetic profile of bismuth under real-life conditions	Study of the safety and pharmacokinetics under real-life conditions (SAPHARY)

3.4. Conclusion

In the eradication of *Helicobacter pylori*, the fixed combination of bismuth subcitrate potassium, metronidazole and tetracycline (PYLERA) administered along with omeprazole for 10 days has been compared with the free combination of amoxicillin, clarithromycin and omeprazole for 10 days (study HPST99-CUS01, carried out in the USA between 1999 and 2000) or 7 days (study PYLHp07-01, carried out in Europe between 2008 and 2009).
These two studies were open, with “blinded” evaluation of the results by central laboratory independent of the study centres.

In these two studies, PYLERA was not inferior in terms of the eradication of *H. pylori* to the free combination amoxicillin/clarithromycin/omeprazole administered for 10 days (92.5% versus 87.1%) or 7 days (93.3% versus 69.6%) in the *per-protocol* analysis.
In the study versus amoxicillin/clarithromycin/omeprazole for 7 days, which corresponds to the strategy currently recommended in France, the ITT analysis demonstrated the superiority of the bismuth potassium/metronidazole/tetracycline combination (79.8% versus 55.4%; difference 24.4%, 95% CI of the difference [15.5; 33.3%]; $p < 0,001$).

The resistance of *H. pylori* to antibiotics only had a slight effect on the efficacy of the fixed bismuth potassium/metronidazole/tetracycline combination. The percentage eradication of strains resistant to metronidazole (90.5% versus 68.3%) and clarithromycin (90.9% versus 2/25) was higher than that obtained with amoxicillin/clarithromycin/omeprazole for 7 days.

Overall, the safety profile was satisfactory in the studies. The most common adverse effects during treatment with the fixed combination of bismuth/metronidazole/tetracycline + omeprazole were gastrointestinal (abnormal/discoloured stools: 17.2% versus 1.9%; abdominal pain: 7.8% versus 3.2%; nausea: 10.6% versus 4%) and neurological (headaches: 7.2% versus 2.4%; dizziness: 4.8% versus 1.3%; somnolence: 3.0% versus 0; asthenia: 4.3% versus 1.1%). Even though there was an increase in transaminases (ASAT: 23.9% and ALAT: 16.6% versus 7.1% and 3.9%), it was transitory and did not involve an increase in bilirubin or changes in liver function.

The plasma bismuth concentration remained below the toxic threshold of 50 µg/l and had returned to below the limit of detection in the majority of patients by week 10.

The clinical development programme and the postmarketing surveillance data from the United States did not provide any evidence of a risk of bismuth-related neurotoxicity in association with PYLERA.

The Transparency Committee takes note of the actions set in place (RMP) to monitor aspects relating to safety of use, in particular monitoring for cases of encephalopathy.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The major role of *Helicobacter pylori* in the development of gastric and duodenal ulcers has been well demonstrated.
In France, the percentage infection with *H. pylori* is currently estimated at 20 to 50% of the adult population. Infection with *H. pylori* very frequently results in the development of chronic gastritis, which is more often than not asymptomatic and which rarely resolves spontaneously. The infection may also cause disequilibrium between aggressive and protective factors at a precise point on the mucosa, at the point of origin of gastric and duodenal ulcers. Thus, about 10% of people infected with *H. pylori* will develop an ulcer and 1% stomach cancer.

PYLERA is intended as a curative or preventive therapy.

The efficacy/adverse effects ratio is high.

It is a first-line therapy.

There are treatment alternatives.

Public health benefit
The burden represented by the complications of infection with *Helicobacter pylori* (gastroduodenal ulcer) can be considered to be moderate.

The availability of a diverse range of antibiotics that permits the control, on a rational basis, of the prescription of antibiotics, the preservation of their efficacy, and limitation of the appearance and spread of bacterial resistance, is a public health need that falls within the framework of established priorities (antibiotics plan 2011-2016).
In view of the current level of resistance of *H. pylori* to clarithromycin in France (> 20%), the propriety medicinal product PYLERA could provide a partial response to this public health need provided that compliance is confirmed in routine medical practice.

However, the absence of data on the recurrence of infections in the medium term, the impact of PYLERA on the prevention of gastrointestinal ulcers and their complications is difficult to quantify.

The propriety medicinal product PYLERA is therefore expected to be of benefit to public health. In view of the uncertainties at this stage, this benefit can only be small.

The actual benefit of this proprietary medicinal product PYLERA is substantial**.**

4.2. Improvement in actual benefit (IAB)

In view of the available data and bearing in mind the current development of resistance to clarithromycin by *H. pylori* in France, the Committee considers that PYLERA provides a minor improvement in actual benefit (level IV) in treatment for the eradication of *Helicobacter pylori*.

4.3. Therapeutic use

Therapeutic strategy

AFSSAPS guidelines (2005)

The eradication of *H. pylori* infection was the subject of AFSSAPS guidelines in 2005. The recommended treatment was:

- **first-line treatments**: proton-pump inhibitor (PPI) + clarithromycin + amoxicillin for 7 days; in case of contraindication of beta-lactams, PPI + clarithromycin + imidazole; in case of contraindication of clarithromycin, PPI + amoxicillin + imidazole,
- **in case of failure**: PPI + amoxicillin + imidazole for 14 days.

However, the levels of resistance in France are currently more than 20% for clarithromycin and 40 to 60% for metronidazole.[12,13,14] There is a clear correlation between failure and resistance of *H. pylori* to antibiotic treatment, particularly for clarithromycin. Therefore, a reduction in the efficacy of these classic triple therapies is increasingly being observed.

Maastricht IV Consensus Conference (2012) [15]

There is an international consensus to adapt the treatment to the local resistance situation (Table 9), particularly with respect to clarithromycin, which is considered high at more than 20%.

Table 9: Principal recommendations of the Maastricht IV Consensus Conference for the treatment of *H. pylori* infection

Recommendation	Level of evidence	Grade of recommendation
In regions of low resistance to clarithromycin, treatments containing clarithromycin are recommended as first line treatments. Quadruple therapy based on bismuth is an alternative.	1a	A
In regions of high resistance to clarithromycin, quadruple therapy containing bismuth is recommended as the first line treatment. If this treatment is not possible, sequential treatment* or quadruple therapy without bismuth** is recommended.	1a	A
The use of high doses of PPI (twice daily) increases the efficacy of triple therapy.	1b	A
Increasing the duration of treatments containing PPI + clarithromycin to 10-14 days increases the success of the eradication by about 5% and may be considered.	1a	A
The PPI + clarithromycin + metronidazole and PPI + clarithromycin + amoxicillin treatments are equivalent.	1a	A
After failure of treatment containing PPI + clarithromycin, quadruple therapy containing bismuth or triple therapy containing levofloxacin may be used.	1a	A

* Sequential treatment = 5 days of treatment with amoxicillin + PPI then 5 days of clarithromycin + metronidazole + PPI

** Quadruple therapy without bismuth = three antibiotics (amoxicillin, clarithromycin and metronidazole) taken simultaneously + PPI

[12] Raymond J, Lamarque D, Kalach N, Chaussade S, Burucoa C. High level of antimicrobial resistance in French Helicobacter pylori isolates. Helicobacter 2010; 15: 21-7.

[13] Megraud F. The challenge of *Helicobacter pylori* resistance to antibiotics: the comeback of bismuth-based quadruple therapy. Ther Advances Gastroenterol 2012; 5: 103-109.

[14] Megraud F, Coenen S, Versporten A, et al. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut. 2012 May 12. [Epub ahead of print]

[15] Malfertheiner P, Megraud F. European *Helicobacter* Study Group. Management of *Helicobacter pylori* infection - the Maastricht IV/ Florence Consensus Report. Gut 2012; 61: 646-64.

Therapeutic use of PYLERA

Because France is considered to be a country with a high level of resistance to clarithromycin, PYLERA is a first-line treatment for the eradication of *H. pylori* in case of ulcerative disease, because its efficacy is not affected by resistance to clarithromycin and to a lesser degree metronidazole. However, because of the burden imposed by the treatment (three capsules four times a day and two doses of PPI per day for 10 days) and the frequency of gastrointestinal and neurological adverse effects, the level of compliance with PYLERA under practical clinical conditions of use is unknown.

The possible alternative to treatment by quadruple therapy containing bismuth is sequential treatment, which combines a PPI in the morning and evening for 10 days with 5 days of amoxicillin 1000 mg x 2/d followed by 5 days of treatment with metronidazole 500 mg x 2/d + clarithromycin 500 mg x 2/d. However, this regimen is complex and there have not been any studies in France, a country with a high percentage of resistance to clarithromycin. Bismuth-free concomitant quadruple therapy combining three antibiotics (amoxicillin, clarithromycin and metronidazole) and a PPI for 10 to 14 days has also been suggested.

Another solution would be to test the bacterial sensitivity, particularly to clarithromycin, on a biopsy, using molecular biological methods, in order to be able to continue to use PPI/clarithromycin/amoxicillin triple therapy in cases of sensitivity to clarithromycin and opt for another strategy in case of resistance.

4.4. Target population

There is little epidemiological data available relating to gastroduodenal ulcers in France. An estimate of the annual incidence of gastrointestinal ulcers in adults would be 2 per 1000,[16] which is equivalent to 97,800 cases. Another estimate cites 70,000 new cases of gastrointestinal ulcers per year in France[17].

About 90% of patients with duodenal ulcers and 70% of patients with gastric ulcers are infected with *H. pylori*. Different treatments are used for ulcers, depending on whether *H. pylori* infection is present. Consequently, tests for the *H. pylori* infection should always be carried out before treatment. If *H. pylori* is eradicated, the risk of recurrence is almost zero.

Bearing in mind that eradication of *H. pylori* has clearly declined and the need for long-term treatment of patients suffering from ulcers, the incidence of ulcers (estimated at around 70,000 to 100,000 cases per year) may be considered a good indicator for the estimation of the target population. In addition, bearing in mind that 70 to 90% of patients with ulcers are infected with *H. pylori*, the target population for PYLERA (ulcerative disease together with *H. pylori* infection) could be estimated at 50,000 to 90,000 cases per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosage given in the Marketing Authorisation.
Because of doubts about treatment compliance with PYLERA under real-life conditions of use and bearing in mind the request for a study made by ANSM (the French drug safety agency) within the framework of the RMP to evaluate its use in routine practice, the Transparency Committee also requests a copy of the results of this study and plans to revise its opinion on the basis of the conclusions reached.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

[16] Popsai D, Sobhani I, Mignon M. Maladie ulcéreuse duodénale et gastrique non compliquée [Uncomplicated duodenal and gastric ulcers]. In: Rambaud JC, ed. Traité de gastro-entérologie [Treatise on gastroenerology]. Paris: Flammarion; 2005. p. 329-346.
[17] Landi B. Maladie ulcéreuse gastro-duodénale chez le sujet âgé. Première partie généralité, signes clinique et endoscopiques. [Gastroduodenal ulcers in elderly patients. First general part, clinical and endoscopic signs] Rev Gériat 2002; 27 (9): 735-40