Part VI: Summary of the Risk Management Plan

This is a summary of the Risk Management Plan (RMP) for Pylera. The RMP details important risks of Pylera, how these risks can be minimized, and how more information will be obtained about Pylera's risks and uncertainties (missing information).
Pylera's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Pylera should be used.
Important new concerns or changes to the current ones will be included in updates of Pylera's RMP.

I. The medicine and what it is used for

Pylera is for the eradication of *H. pylori* and prevention of relapse of peptic ulcers in patients with active or a history of *H. pylori* associated ulcers, in combination with omeprazole. It contains bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride as the active substances and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Pylera, together with measures to minimise such risks and the proposed studies for learning more about Pylera's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without a prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimization measures*.

In addition to these measures, information about adverse reactions is collected continuously and is regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Pylera are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered.
Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of relation to the use of Pylera. Potential risks are concerns for which an

association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 37 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Candidiasis and other superinfections Peripheral neuropathy Encephalopathy
Important potential risks	Lack of efficacy Use in special populations (as a risk factor for peripheral neuropathy and encephalopathy) Hepatotoxicity Seizure Pancreatitis
Missing information	None

II.B Summary of important risks

Table 38 Summary of important risks

Important Identified risk: Candidiasis and other superinfections	
Evidence for linking the risk to the medicine	Phase III CSR: HPST 99 INT01, HPST99-CUS01 and PYLHp07-01 Phase IIIb listings and tabulations: MA-PY-Hp09-01 Safety database Literature : Yap *et al*, 2009 ; HPA, 2010 ; Clabots *et al*, 1992 ; Curry, 2010 ; Concia *et al.*, 2009 ; Reinke and Messick, 1994 ; Iser *et al.*, 1994 ; Karczewska *et al.*, 2009 Vazquez *et al.*, 1995 ; Richardson *et al.*, 2005 ; Conde-Rosa et *al, 2010 ;* Loo *et al*, 2005 ; Dallal *et al*, 2002

Risk factors and risk groups	The main risk factors for invasive candidiasis are neutropenia, exposure to broad spectrum antimicrobial agents, mucosal colonization with *Candida* spp, indwelling vascular catheters, previous surgery and chemotherapy [Concia *et al*., 2009]. Other important risk factors are diabetes [Vazquez *et al.*, 1995] and immunosuppression such as after HIV infection or after the use of specific drugs [Richardson *et al.*, 2005]. Concerning pseudomembranous colitis, patients at higher risk are those presenting advanced age (especially over 65), inflammatory bowel disease, a prolonged hospital stay and those taking antibiotics [Curry, 2010].
Risk minimisation measures	Routine RMMs only
Identified Risk: Peripheral neuropathy	
Evidence for linking the risk to the medicine	Phase III CSR: HPST 99 INT01, HPST99-CUS01 and PYLHp07-01 Phase IIIb listings and tabulations: MA-PY-Hp09-01 Safety database Literature: Mold et al, 2004; Velasco and Bruna, 2010; Kapoor, Chandra et al. 1999; Arne-Bes 2004; Kountouras, Deretzi et al. 2005; Chiò et al, 2003; Sarma and Kamath 2005; Beghi and Monticelli, 1998; Vittadini et al, 2001; Chaudhry 2008; Demir et al. 2008; Ghabaee, Ghanbarian et al. 2010
Risk factors and risk groups	The main risk factors for invasive candidiasis are neutropenia, exposure to broad spectrum antimicrobial agents, mucosal colonization with *Candida* spp, indwelling vascular catheters, previous surgery and chemotherapy [Concia *et al*., 2009]. Other important risk factors are diabetes [Vazquez *et al.*, 1995] and immunosuppression such as after HIV infection or after the use of specific drugs [Richardson *et al.*, 2005]. Concerning pseudomembranous colitis, patients at higher risk are those presenting advanced age (especially over 65), inflammatory bowel disease, a prolonged hospital stay and those taking antibiotics [Curry, 2010].
Risk minimisation measures	Routine RMMs only
Identified Risk: Encephalopathy	
Evidence for linking the risk to the medicine	Phase III CSR: HPST 99 INT01, HPST99-CUS01 and PYLHp07-01 Phase IIIb listings and tabulations: MA-PY-Hp09-01

	Safety database Literature: (Lechat, Palliere et al. 1976; Martin-Bouyer 1978; Lechat and Kisch 1986; Bader 1987; Hespe, Staal et al. 1988; Bradley, Singleton et al. 1989; Slikkerveer and de Wolff 1989; Gorbach 1990; Playford, Matthews et al. 1990; Menge 1992; Anonymous 1997; Fauci 2008)
Risk factors and risk groups	Since encephalopathy has not been reported with Pylera during the clinical developmental program and post-marketing experience, no risk groups or risk factors have been identified. However, several risk factors have been described in the literature with the use of bismuth salts.
Risk minimisation measures	Routine RMMs
Additional pharmacovigilance activities	Targeted Follow-up Questionnaires: Pylera Neurological Disorders and Bismuth Testing (France) Pylera Neurological Disorders and Bismuth Testing (outside France)
Important Potential Risk: Lack of efficacy	
Evidence for linking the risk to the medicine	Phase I CSR: HLD-PO-241, HLD-PO-180 Phase III CSR: HPST 99 INT01, HPST99-CUS01 and PYLHp07-01 Safety database Literature: Malfertheiner *et al*, 2007; Chey *et al*, 2007; Gisbert *et al*, 2007; Egan *et al*, 2007; Fischbach *et al*, 2004; Houben *et* al, 1999; Wolle *et al*, 2002; Koivisto *et al*, 2004; Osato *et al*, 2001; van der Wouden *et* al, 1999; Mégraud and Corti, 2009; Mégraud, 2004; Ford and Moayyedi, 2003; Marshall and Warren, 1984; Morgner *et al*, 2006; Jodlowski *et* al, 2008; Luther *et al*, 2010; Wu and Shen, 2009; Suerbaum and Michetti, 2002; Kwok *et al*, 2008; Fuccio *et al*, 2009
Risk factors and risk groups	Both European and American guidelines recognize the increasing resistance to clarithromycin as the main risk factor for treatment failure with the clarithromycin-based triple therapies, so that resistance to this agent needs to be taken into account when deciding on the type of antibiotics to be used [Malfertheiner *et* al, 2007; Chey *et al*, 2007]. The most important predictors of treatment failure are antibiotic resistance and poor adherence to the drug regimen [Gisbert *et al*, 2007; Chey *et* al, 2007; Egan *et al*, 2007; Fischbach *et al*, 2004].
Risk minimisation measures	Routine RMMs only

Additional pharmacovigilance activities	Targeted Follow-up Questionnaires: Pylera Eradication Therapy Failure
Important Potential Risk: Hepatotoxicity (including liver enzymes values increased)	
Evidence for linking the risk to the medicine	Phase III CSR and pooled data listing: HPST 99 INT01, HPST99-CUS01 and PYLHp07-01 Phase IIIb listings and tabulations: MA-PY-Hp09-01 Safety database Literature: Björnsson, 2010 Sgro et al., 2002; Mehta et al., 2010; Tabak et al., 2003; Aithal and Day, 2007; Treeprasertsuk et al., 2010; Björnsson, 2009
Risk factors and risk groups	Main risk factors for drug hepatotoxicity in general are female sex, advanced age, existence of certain genetic polymorphisms that predispose the patient to a higher risk of liver toxicity, pre-existent liver disease and malnutrition. Specifically, for tetracycline, the main risk factors are female gender, pre-existing renal failure and pre-existing liver disease (Mehta *et al*., 2010). No specific risk factors for liver toxicity after the use of metronidazole are known to date (Tabak *et al*., 2003).
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Seizure	
Evidence for linking the risk to the medicine	Literature : Okuda et al. 2004, Oztuk 2007, Asadi-Pooya 2012, Abdul Razak 2012, Kushner 2001, Buge et al. 1981, Kuriyama et al. 2011, Ahmed et al. 1995
Risk factors and risk groups	Risk factors for the development of seizures include electrolyte disturbances, decreased renal function, advanced age and concomitant treatment with another medication that can reduce the seizure threshold. Patients with a history of seizures are also at risk (Kushner 2001).
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Pancreatitis	
Evidence for linking the risk to the medicine	Scientific literature The IMP study (involving analysing all serious French cases of AE reported to APTALIS and recorded in the National Pharmacovigilance Database (BNPV) from 01/07/2015 to 30/11/2016)
Risk factors and risk groups	The risk factors of pancreatitis include: Age, sex, race, lifestyle factors (e.g. alcohol, smoking, diet), other comorbidities (e.g., gallstones, obesity, inflammatory bowel disease and diabetes) and concomitant use of certain drugs (e.g., Angiotensin-converting enzyme inhibitors, statins, oral contraceptives/hormone replacement therapy, diuretics,

	antiretroviral therapy, valproic acid, and hypoglycaemic agents) (Lauret et al. 2015, Jones et al. 2015).
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Use in special populations (as a risk factor for peripheral neuropathy and encephalopathy)	
Evidence for linking the risk to the medicine	In the literature, 1 case of encephalopathy was reported in a 68-year-old male patient with chronic renal failure, diabetes, hypertension and ischaemic heart disease [Playford *et al*, 1990]. He was administered 864 mg DeNol (bismuth tripotassium dicitrate)/day, twice the recommended dose, for 2 months for gastritis. Whole blood bismuth concentrations were at 880 µg/L. Fifty days after stopping DeNol, EEG and mental function recovered completely and whole blood bismuth concentration fell to 46 µg/L.
Risk factors and risk groups	The use of Pylera in special population is considered as an important potential risk and as a risk factor for peripheral neuropathy, i.e.: Use of Pylera in renal impaired population, in hepatic impaired population or in population with central nervous system diseases (including epilepsy). Bismuth digestive absorption can be increased by external factors (high dosage, physical properties of bismuth compound, concomitant substances that increase bismuth dissolution such as liquids) and internal factors (patients who have digestive disorders and chronically constipated patients, pathological alterations of the intestinal transit or intestinal mucosa status since intestinal bacteria could be involved in the bismuth neurotoxicity) [Slikkerveer and Wolff, 1989; Lechat and Kisch, 1986].
Risk minimisation measures	Routine RMMs only
Additional pharmacovigilance activities	Targeted Follow-up Questionnaires: Pylera Neurological Disorders and Bismuth Testing (France) Pylera Neurological Disorders and Bismuth Testing (outside France)

II.C Post-authorisation development plan

II.C.1 Studies that are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Pylera.

II.C.2 Other studies in the post-authorisation development plan

Not applicable