SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pylera 140 mg/125 mg/125 mg capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 140 mg of bismuth subcitrate potassium (equivalent to 40 mg bismuth oxide),

125 mg of metronidazole and 125 mg of tetracycline hydrochloride.

Excipients with known effect: Each capsule contains 61 mg of lactose monohydrate and 32 mg of potassium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (Capsule)

Elongated, white, opaque capsule with 'BMT' printed on the cap in red ink. It contains a white powder plus a smaller white opaque capsule containing a yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

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 after 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 morning meal and evening meal doses of Pylera for the full 10 days of therapy.

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 after a snack)	3	0

Missed doses can be made up by extending the normal dosing schedule beyond 10 days until all the medicinal product has been consumed. Patients should not take two doses at one time. If more than 4 consecutive doses (1 day) are missed, the prescribing physician should be contacted.

Patients with hepatic or renal impairment

Pylera is contraindicated in patients with renal or hepatic impairment (see sections 4.3 and 4.4). The safety and effectiveness of Pylera in hepatic or renal impaired patients has not been evaluated.

Older people

Experience in older people 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 medicinal therapies should be considered when prescribing Pylera for this patient population.

Paediatric population

Pylera is contraindicated in children less than 12 years of age (see section 4.3) and not recommended in children 12 to 18 years of age.

Method of administration

For oral use. The capsules should not be opened but swallowed whole. Pylera and omeprazole should be taken after a meal while seated with a full glass of water (250 ml), particularly with the bedtime dose, to reduce the risk of oesophageal ulceration by tetracycline hydrochloride (see section 4.8). Patients should not lay down immediately after Pylera and omeprazole intake.

4.3 Contraindications

- Pregnancy and breast-feeding
- Paediatric population (up to 12 years of age)
- Renal or hepatic impairment
- Hypersensitivity to the active substances, other nitroimidazole derivatives, or to any of the excipients listed in section 6.1.
- Patients with Cockayne syndrome (see section 4.8)

4.4 Special warnings and precautions for use

There have been rare reports of encephalopathy associated with excessive doses of various bismuth- containing products with prolonged treatment, reversible with discontinuation of therapy. Also, very rare cases of encephalopathy have been reported with metronidazole (see section 4.8.c). Post marketing cases of encephalopathy associated with the use of Pylera have been received.

Peripheral neuropathy has been reported in patients given metronidazole, usually for long periods. However, cases of peripheral neuropathy have also been reported with Pylera. If abnormal neurologic signs appear, prompt discontinuation of Pylera is required. Pylera should be administered with caution to patients with diseases of the central nervous system (see section 4.8).

Oral candidiasis, vulvovaginitis, and pruritus ani, mainly due to overgrowth with *Candida albicans*, may occur during therapy with tetracycline and may require treatment with an antifungal agent. There may be associated overgrowth of resistant coliform organisms, such as *Pseudomonas spp.* and *Proteus spp.*, causing diarrhoea. More serious, enterocolitis due to superinfection with resistant staphylococci and pseudomembranous colitis due to *Clostridium difficile* have occasionally been reported with the use of tetracycline. If superinfection occurs, Pylera should be discontinued and appropriate therapy should be instituted (see section 4.8).

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs. Treatment should be discontinued at the first evidence of skin erythema.

Administration of adequate amounts of fluid, particularly with the bedtime dose of tetracycline hydrochloride is recommended to reduce the risk of oesophageal irritation and ulceration (see section 4.8).

Metronidazole should be used with caution in patients with evidence, or history, of blood dyscrasia. A mild leukopenia has been observed in rare cases (see section 4.8) with prolonged use of metronidazole.

The dose of oral anticoagulants such as warfarin may require reduction during the treatment with Pylera (metronidazole may prolong prothrombin time). Prothrombin times should be monitored. There is no interaction with heparin (see section 4.5). Omeprazole may delay the elimination of warfarin, a reduction of the warfarin dose may be necessary.

QT prolongation has been reported when metronidazole is concomitantly administered with medicinal products, which have both a potential for prolonging the QT interval and a potential for increased plasma levels secondary to drug-drug interactions with metronidazole (see 4.5).

Alcoholic beverages should not be consumed during therapy with Pylera and for at least 24 hours after completing the treatment (see section 4.5).

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracycline. The usual clinical manifestations are headache and blurred vision. While this condition and related symptoms usually resolve soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists (see sections 4.8 and 4.5 for interaction with retinoids).

Myasthenic syndrome has been reported rarely with tetracycline. Care is advisable in patients with myasthenia gravis, who may be at risk of worsening of the condition (see section 4.8).

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity. Therefore, the use of methoxyflurane in patients taking Pylera should be avoided.

Pylera contains approximately 96 mg of potassium per dose (3 capsules containing 32 mg of potassium each). To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

It also contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

Bismuth absorbs x-rays and may interfere with x-ray diagnostic procedures of the gastrointestinal tract.

Bismuth may cause a temporary and harmless darkening of the stool. However, this does not interfere with standard tests for occult blood.

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide (NAD). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed with Pylera. As such the following section outlines the interactions observed with the different components of Pylera as reported in their respective Summary of Product Characteristics or as reported in the literature.

The need for other concomitantly given medication in patients receiving Pylera should be checked before treatment. Although no specific interaction with the combination has been detected, patients on a high number of concomitant medications are generally at higher risk to experience undesirable effects and should therefore be treated with caution.

Interactions with bismuth

Ranitidine enhances the absorption of bismuth. Omeprazole increases the absorption of bismuth.

Therefore, it is recommended to take Pylera and omeprazole after food in order to reduce the absorption of bismuth.

Interactions with metronidazole

Lithium

Based on a few cases, metronidazole may precipitate signs of lithium toxicity in patients receiving high doses of lithium. Strict monitoring of lithium levels is recommended in such patients.

Alcohol/disulfiram

Metronidazole has a well-documented disulfiram-like reaction with alcohol (abdominal cramps, nausea, vomiting, headache, flushing). Psychotic reactions have been reported in alcoholic patients who are using metronidazole and have used disulfiram within the previous 2 weeks.

Anticoagulants

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. Therefore, monitoring with appropriate adjustment of the anticoagulant dose is warranted during treatment with Pylera.

Phenytoin, phenobarbital

The simultaneous administration of medicinal products that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels. Impaired clearance of phenytoin has also been reported in such situations. The clinical significance of reduced systemic exposure to metronidazole is unknown as the relative contribution of systemic versus local antimicrobial activity against *Helicobacter pylori* has not been established.

5-Fluorouracil

Metronidazole reduces the clearance of 5-fluorouracil and can therefore result in increased toxicity of 5-fluorouracil.

Cyclosporin

Patients receiving cyclosporin are at risk of elevated cyclosporin serum levels. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Busulfan

Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

Concomitant products that prolong QT interval and of which metabolism may be inhibited by metronidazole:
The combination of metronidazole with compounds being metabolised by CYP3A4 or CYP2C9 and prolonging the QT interval should be avoided (e.g. ondansetron, amiodarone, methadone, domperidone).

Interactions with tetracycline

Methoxyflurane

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Anticoagulants

Tetracycline has been shown to decrease plasma prothrombin activity. Therefore, frequent monitoring of anticoagulant therapy with appropriate adjustment of the anticoagulant dose is warranted with initiation of Pylera.

Penicillin

Since bacteriostatic medicinal products, such as the tetracycline class of antibiotics, may interfere with the bactericidal action of penicillin, it is not advisable to administer these medicinal products concomitantly.

Antacids, iron preparations and dairy products

Absorption of tetracycline is impaired by antacids containing aluminium, calcium or magnesium, preparations containing iron, zinc, or sodium bicarbonate, or dairy products. The clinical significance of reduced systemic exposure to tetracycline is unknown as the relative contribution of systemic versus local antimicrobial activity against *Helicobacter pylori* has not been established. Therefore, these products should not be used concomitantly with Pylera.

Retinoids

An increased incidence of benign intracranial hypertension has been reported when retinoids and tetracyclines are given together; such use should be, therefore, avoided (see section 4.4). Discontinuing retinoid therapy for the short duration of Pylera treatment should be considered.

Atovaquone

Tetracycline may decrease plasma atovaquone concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

Based on human experience tetracycline hydrochloride (a component of Pylera) causes effects on teeth and skeletal development when administered during pregnancy.

Pylera is contraindicated during pregnancy (see section 4.3). There are no data from the use of Pylera in pregnant women.

There are no animal data with respect to the effects of bismuth subcitrate potassium. Animal studies are insufficient with respect to the effects of colloidal bismuth subcitrate (colloidal bismuth subcitrate is similar to bismuth subcitrate potassium in terms of physicochemical, structural, biological (*in vitro*) and pharmacokinetic characteristics) and metronidazole on reproductive toxicity.

Fertility

Animal studies with metronidazole and tetracycline hydrochloride (components of Pylera) have shown evidence of impairment of male fertility. There are no animal data with respect to the effects of bismuth subcitrate potassium. Animal studies are insufficient with respect to the effects of colloidal bismuth subcitrate (colloidal bismuth subcitrate is similar to bismuth subcitrate potassium in terms of physicochemical, structural, biological (*in vitro*) and pharmacokinetic characteristics) on reproductive toxicity (see section 5.3).

Breast-feeding

Metronidazole is excreted in human milk in concentrations similar to those found in plasma.

It is unknown whether bismuth subcitrate potassium or its metabolites are excreted in human milk.

Tetracycline hydrochloride is excreted in human milk and effects on teeth have been shown in breastfed newborns/infants of women treated with tetracycline hydrochloride. Pylera is contraindicated during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

An influence on the ability to drive and use machines is not expected from the known pharmacodynamic properties of the compounds of which Pylera is composed. However, clinical studies to document the absence of such effects have not been conducted.

Convulsive seizures and dizziness have been reported in patients treated with metronidazole. Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracycline, the clinical manifestations of which include transient blurred vision (see section 4.8). Patients should be warned about the potential for these adverse reactions and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

a. Summary of the safety profile

The adverse reactions reported with Pylera in combination with omeprazole during controlled clinical trials were consistent with the known safety profile of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride when given as separate products.

The most commonly reported adverse reactions (very common) during treatment with Pylera are, in decreasing order of frequency: abnormal faeces, diarrhoea, nausea, and dysgeusia (including metallic taste).

Severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome; potentially fatal) have been reported with the use of Pylera and the individual components, metronidazole and tetracycline. The occurrence of severe cutaneous adverse reactions require immediate discontinuation of Pylera.

Pseudomembranous colitis (*Clostridium difficile* colitis) and peripheral neuropathy have been reported with the use of Pylera (see section 4.4).

b. Tabulated list of adverse reactions

Adverse reactions are presented from pooled data of three phase III controlled clinical trials (540 patients exposed to Pylera) and post-marketing experience (including spontaneous, regulatory and literature reports).

Adverse reactions are ranked under headings of frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class Preferred Term	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Not known**
Infections and infestations		Vaginal infection	Candidiasis, oral candidiasis, vaginal candidiasis	Pseudomembranous colitis
Immune system disorders			Drug hypersensitivity	
Metabolism and nutrition disorders		Anorexia, decreased appetite		
Psychiatric disorders			Anxiety, depression, insomnia	
Nervous system disorders	Dysgeusia (including metallic taste*)	Headache, dizziness, somnolence	Hypoesthesia, paraesthesia, amnesia, tremor	Peripheral neuropathy, aseptic meningitis; Cerebellar syndrome
Eye disorders			Blurred vision	
Ear and labyrinth disorders			Vertigo	
Gastrointestinal disorders	Diarrhoea, nausea, abnormal faeces (including black stools*)	Vomiting, abdominal pain (including abdominal pain upper), dyspepsia, constipation, dry mouth, flatulence	Tongue oedema, mouth ulceration, stomatitis, abdominal distension, eructation, tongue discolouration	

System Organ Class Preferred Term	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Not known**
Hepatobiliary disorders		Alanine aminotransferase increased, aspartate aminotransferase increased		
Skin and subcutaneous tissue disorders		Rash (including rash maculo-papular, rash pruritic)	Urticaria, pruritus	Blister, Skin exfoliation, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome), DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms)
Renal and urinary disorders		Chromaturia		
General disorders and administration site conditions		Asthenic conditions**	Chest pain, chest discomfort	

* Lowest Level Term (LLT); ** High-Level Term (HLT)
MedDRA Version 11.0

c. Description of selected adverse reactions

Black stools and tongue discolouration may occur with bismuth compounds, due to conversion to bismuth sulfide in the gastrointestinal tract; stomatitis has been attributed to bismuth salts but has also been reported with the use of metronidazole.

Like other antimicrobial agents, tetracycline may lead to development of superinfections. Candidiasis (oral and vaginal) is probably due to tetracycline.

Dizziness, dysgeusia, headache and chromaturia (darkening of the urine) are most likely attributable to metronidazole.

Reversible and transient elevations of transaminases have been observed during clinical trials with Pylera.

Cerebellar syndrome (eg. ataxia, dysarthria, gait impairment, nystagmus and tremor), which may resolve upon discontinuation of the drug, have been observed with Pylera.

Other Important Adverse Reactions from Labelling for the individual Components of Pylera

Adverse reactions reported to occur with bismuth compounds

- Encephalopathy was associated with the usage of high doses of different bismuth salts over a prolonged period of time.

Adverse reactions reported to occur with metronidazole

- Reversible leuco-neutropenia in cases of prolonged treatment; rarely, reversible thrombocytopenia;
- Convulsive seizures have been associated with metronidazole therapy (usually in high doses or in patients with renal impairment).
- Peripheral neuropathy has been reported in patients given metronidazole, usually for long periods. Stopping metronidazole or lowering the dose usually results in complete resolution or improvement of the neuropathy but in some patients, it may persist despite these measures.
- Anaphylaxis, dysuria, cystitis, incontinence, pancreatitis and pseudomembranous enterocolitis.
- Very rare cases of encephalopathy, cholestatic hepatitis and jaundice have been reported with metronidazole.
- Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.3).

Adverse reactions reported to occur with tetracycline hydrochloride

- Pseudomembranous colitis caused by overgrowth of *Clostridium difficile* is a potential complication with the use of tetracycline; other superinfections can occur, as with other antibiotics.
- In some cases, liver failure was reported in patients receiving large doses of tetracycline and in patients with renal impairment.
- Renal dysfunction has been reported with tetracycline, particularly exacerbation of dysfunction in those with pre-existing renal impairment. These effects are related to dose. Acute renal failure and interstitial nephritis have occurred rarely.
- Permanent discoloration of teeth may occur during tooth development. Enamel hypoplasia has also been reported.
- Oesophageal ulceration has been reported with tetracycline, particularly after ingestion of capsules or tablets with insufficient water at bedtime.
- Although rare, haemolytic anaemia, thrombocytopenia, thrombocytopenic purpura, neutropenia, and eosinophilia have been reported with the use of tetracycline.
- Pseudotumor cerebri (benign intracranial hypertension) has been reported in adults given tetracycline; bulging fontanels have been reported in tetracycline treated infants.
- Occasionally, increased muscle weakness (Myasthenic syndrome) has been reported with tetracycline in patients with myasthenia gravis.
- Photosensitivity which has been reported with most tetracycline antibiotics, occurs very rarely with tetracycline; it appears to be phototoxic rather than

photoallergic in nature. Paraesthesia may be an early sign of impending phototoxicity.

- Pharyngitis, anaphylaxis, exfoliative dermatitis, and pancreatitis.

d. Paediatric population

Pylera is contraindicated in patients less than 12 years of age and should not be used in children aged 12 to 18 years.

e. Other special populations

Older people

Experience in older people is limited. No specific safety concerns have been identified.

Hepatic impairment

In clinical trials with Pylera, transient mild to moderate increases in liver enzymes have been observed. Pylera is contraindicated in patients with hepatic impairment (see section 4.3).

Renal impairment

Pylera is contraindicated in patients with renal impairment (see section 4.3). No renal failure has been attributed to Pylera in clinical trials.

f. Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In case of an overdose, patients should contact a physician, poison control centre or emergency department.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations for the eradication of *Helicobacter pylori*, ATC code: A02BD08

Pylera is a triple fixed combination capsule containing bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride for the eradication of *H. pylori* in combination with omeprazole (quadruple therapy).

Mechanism of action

Bismuth

The exact effect of bismuth in the treatment of *H. pylori* infections is still unknown. It appears to be related to direct toxicity on membrane function, inhibition of protein and cell wall synthesis, inhibition of urease enzyme activity, prevention of cytoadherence, ATP synthesis and a non-specific competitive interference with iron transport.

Metronidazole

The antimicrobial mechanism of action of metronidazole depends on the reduction of its nitro moiety by nitroreductase and other reductases to nitro anion radicals. These radicals damage the DNA of the bacteria, ultimately resulting in cell death.

Tetracycline

Tetracycline binds specifically to the 30S ribosome and prevents access of tRNA to mRNA-ribosome complex and thus interfere with protein synthesis.

Relationship between pharmacokinetics and pharmacodynamics

Bismuth

The PK/PD relationship of bismuth subcitrate has not been established.

Metronidazole

Efficacy is mainly dependent upon the Cmax (maximum serum concentration): MIC (minimum inhibitory concentration) ratio of the pathogen and the AUC (area under the curve): MIC ratio of the pathogen, respectively.

Tetracycline

Efficacy is mainly dependent upon the AUC (area under the curve): MIC ratio of the pathogen.

Mechanism(s) of resistance

Bismuth

Resistance to bismuth among Gram-negative bacteria has been shown to be dependent upon iron and its uptake. Resistance to the inhibitory action of bismuth is inversely related to iron concentration and strongly dependent on iron transport mechanisms.

Metronidazole

In *Helicobacter pylori* resistance is related to mutations of the NADPH-nitroreductase coding gene. These mutations prevent the reduction of the nitro moiety of metronidazole by the nitroreductase.

Tetracycline

The three main resistance mechanisms that have been described are:

- Decreased accumulation of tetracycline as a result of either decreased antibiotic influx or acquisition of an energy-dependent efflux pathway,
- Decreased access of tetracycline to the ribosome because of the presence of ribosome protection proteins, and
- Enzymatic inactivation of tetracyclines.

There is a complete cross-resistance between metronidazole and other Imidazoles and between tetracycline and other tetracyclines.

Breakpoints

Bismuth

Species-related Breakpoints for bismuth and *H. pylori* have not been set by EUCAST (European Committee on Antimicrobial Susceptibility Testing).

Metronidazole

Testing of metronidazole is performed by using the usual dilution series. The following minimum inhibitory concentrations were determined for sensitive and resistant micro-organisms for metronidazole:

EUCAST Breakpoints:

Species	**Sensitive**	**Resistant**
Helicobacter pylori	≤ 4,0 mg/l	> 4,0 mg/l

* based mainly on serum pharmacokinetics

Tetracycline

Species-related Breakpoints for tetracycline and *H. pylori* have not been set by EUCAST. However, a resistance breakpoint for tetracycline and *H. pylori* of 4 mg/l has been used.

Prevalence of acquired resistance

The prevalence of resistance varies geographically and with time for *Helicobacter pylori*. Data on the local resistance information are thus desirable, particularly in order to ensure adequate treatment of severe infections. If the local resistance situation puts the efficacy of Pylera in doubt, expert therapeutic advice should be sought. Particularly in cases of severe infection or unsuccessful therapy, a microbiological diagnosis with confirmation of the micro-organism and its sensitivity to the active ingredients of Pylera should be undertaken.

Currently, the resistance rate of *Helicobacter pylori* regarding tetracycline is considered to be less than 5% while the resistance rate regarding metronidazole lies between approximately 30% and 50%. Clinical data reveal a slight reduction of the eradication rate of *H. pylori* after treatment with Pylera in patients with metronidazole-resistant strains.

Clinical efficacy and safety

Two comparative trials have been conducted, one in Europe (pivotal) and one in the US (supportive), comparing Pylera in combination with omeprazole treatment for 10 days with the standard treatment regimen omeprazole, amoxicillin and clarithromycin (OAC) for 7 and 10 days, respectively. Both studies were randomized, parallel group, open label, active controlled, non-inferiority trials and included subjects with confirmed *H. pylori* infection. The results are summarised in the table below. Compliance was greater than 95% in both treatment groups in both studies.

In order to evaluate the impact of antibiotic resistance, biopsies were taken for culture and resistance of the bacterial strains to clarithromycin and metronidazole was tested. The minimum inhibitory concentration (MIC) defining sensitivity was ≤ 8 µg/ml for metronidazole and < 1 µg/ml for clarithromycin. The results indicate that Pylera is efficacious regardless of resistance of the bacterial strain to metronidazole or clarithromycin.

The impact of ulcers on treatment efficacy was also evaluated in the pivotal European study. The efficacy of Pylera was similar in those patients with presence or past history of peptic ulcers and those without.

Eradication Rates in Controlled Studies using Pylera Capsules (ITT & PP)								
	ITT/MITT				**PP**			
	Pivotal study for EU		**Supportive study**		**Pivotal study for EU**		**Supportive study**	
Treatments	Pylera + Ome-prazole	OAC	Pylera + Ome-prazole	OAC	Pylera + Ome-prazole	OAC	Pylera + Ome-prazole	OAC
Treatment duration	10 days	7 days	10 days	10 days	10 days	7 days	10 days	10 days
Number evaluable for ITT/MITT/PP	218	222	138	137	178	161	120	124
Eradicated, n (%)	174 (79.8%[a] 92.6%[b])	123 (55.4%[a] 67.6%[b])	121 (87.7%)	114 (83.2%)	166 (93.3%)	112 (69.6%)	111 (92.5%)	108 (87.1%)
Eradication rates in patients with peptic ulcer	18/20 (90.0%)	18/29 (62.1%)	ND	ND	18/19 (94.7%)	15/18 (83.3%)	ND	ND
Eradication rates in non-ulcer dyspepsia	155/196 (79.1%)	103/189 (54.5%)	ND	ND	147/158 (93.0%)	95/141 (67.4%)	ND	ND
Eradication rates for:								
Metronidazole resistant	40/48 (83.3%)	31/54 (57.4%)	41/51 (80.4%)	ND	38/42 (90.5%)	28/41 (68.3%)	38/44 (86.4%)	ND
Metronidazole sensitive	101/123 (82.1%)	70/120 (58.3%)	68/74 (91.9%)	ND	98/103 (95.1%)	64/90 (71.7%)	61/64 (95.3%)	ND

Clarithromycin resistant	33/38 (86.8%)	2/29 (6.9%)	ND	3/14 (21.4%)	30/33 (90.9%)	2/25 (8.0%)	ND	3/13 (23.1%)
Clarithromycin sensitive	108/133 (81.2%)	99/145 (68.3%)	ND	93/101 (92.1%)	106/112 (94.6%)	90/106 (84.9%)	ND	88/93 (94.6%)

ITT = Intent to treat. MITT = Modified intent to treat. ND = Not determined. PP = Per Protocol
[a] Missing values imputed as non-eradication. [b] Observed cases analysis.

Safety data from these trials are included in the pooled information in section 4.8.

Paediatric population

The European Medicines Agency has waived the obligation to conduct studies with Pylera in all subsets of the paediatric population on the grounds that the specific medicinal product is likely to be unsafe (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Bismuth subcitrate potassium (bismuth)

Bismuth subcitrate potassium has a relatively long elimination half-life in plasma and blood, therefore accumulation is observed following repeated 4 dosing of Pylera administered concurrently with omeprazole 20 mg 2 times a day for 10 days. Steady state plasma and blood concentrations of bismuth were generally attained by Day 4. Average steady state plasma and blood concentrations of bismuth on Day 10 were below 50 μg/l in all subjects. However, plasma and blood concentrations of bismuth above 50 μg/l were sporadically seen in a proportion of subjects (12 and 8 out of 28 subjects, for plasma and blood concentrations, respectively), which were above 100 μg/l in 2 subjects (1 subject for both blood and plasma, and 1 subject for plasma only), although the elevated levels were transient and observed for less than an hour on each occasion.

There were no marked differences between plasma and blood concentrations of bismuth on each sampling occasion up to Day 10 of dosing and at steady state on Day 10, demonstrating distribution of bismuth into the blood cells compartment. The apparent terminal elimination half-life (T½el) of bismuth in plasma was estimated between 21 and 90 hours. In contrast, due to the possible association of bismuth with blood cells, the T½el of bismuth in blood was longer (estimated between 192 to 605 hours in individual subjects).

Metronidazole

Following oral administration, metronidazole is well absorbed, with peak plasma concentrations occurring between 1 and 2 hours after administration. Plasma concentrations of metronidazole are proportional to the administered dose, with oral administration of 500 mg producing a peak plasma concentration of approximately 12 μg/ml.

Metronidazole appears in the plasma mainly as unchanged compound with lesser quantities of the 2-hydroxymethyl metabolite also present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Metronidazole also appears in cerebrospinal fluid, saliva, and breast milk in concentration similar to those found in plasma.

The average elimination half-life of metronidazole in normal volunteers is 8 hours. The major route of elimination of metronidazole and its metabolites is via the urine (60% to 80% of the dose), with faecal excretion accounting for 6% to 15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(β-hydroxyethyl) 2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 ml/min/1.73m3.

Decreased renal function does not alter the single dose pharmacokinetics of metronidazole. In patients with decreased liver function, plasma clearance of metronidazole is decreased.

Tetracycline hydrochloride

Tetracycline is absorbed (60%-90%) in the stomach and upper small intestine. The presence of food, milk or cations may significantly decrease the extent of absorption. In the plasma, tetracycline is bound to plasma proteins in varying degrees. It is concentrated by the liver in the bile and excreted in the urine and faeces at high concentrations in biologically active form.

Tetracycline is distributed into most body tissues and fluids. It is distributed into the bile and undergoes varying degrees of enterohepatic recirculation. Tetracycline tends to localize in tumors, necrotic or ischaemic tissue, liver and spleen and form tetracycline-calcium orthophosphate complexes at sites of new bone formation or tooth development. Tetracycline readily crosses the placenta and is excreted in high amounts in breast milk.

Pylera capsules

The clinical significance of systemic, as compared to local, active substance concentrations for antimicrobial activity of Pylera against *Helicobacter pylori,* has not been established. A comparative bioavailability study of metronidazole (375 mg), tetracycline (375 mg) and bismuth subcitrate potassium (420 mg, equivalent to 120 mg bismuth oxide (Bi2O3)) administered as Pylera or as 3 separate capsule formulations administered simultaneously was conducted in healthy male volunteers. The pharmacokinetic parameters for the individual active substances, when administered as separate capsule formulations or as Pylera were similar.

The pharmacokinetic parameters for metronidazole, hydrochloride and bismuth were also determined when Pylera was administered under fasting and fed conditions. Food reduced the systemic absorption of all three Pylera components, with AUC values for metronidazole, tetracycline hydrochloride and bismuth being reduced by

6%, 34% and 60%, respectively. Reduction in the absorption of all three Pylera components in the presence of food is not considered to be clinically significant. The increased gastric retention time is likely to be beneficial, as it likely prolongs the exposure of *H. Pylori* to bismuth, metronidazole and tetracycline hydrochloride. Pylera should be given after meals (breakfast, lunch and evening meal) and at bedtime (preferably with a snack), in combination with omeprazole twice a day (breakfast and evening meal) (see section 4.2).

Omeprazole capsules

The effect of omeprazole on bismuth absorption was assessed in 34 healthy volunteers given Pylera (qid) with or without omeprazole (20 mg bid) for 6 days. In the presence of omeprazole, the extent of absorption of bismuth from Pylera was significantly increased, compared to when no omeprazole was given. In the absence of omeprazole Cmax and AUC are respectively 8.1 (84% CV) and 48.5 (28% CV). Whereas in the presence of omeprazole the Cmax and AUC respectively 25.5 (69% CV) and 140.9 (42% CV). Concentration-dependent neurotoxicity is associated with long-term use of bismuth and not likely to occur with short-term administration or at steady state blood concentrations below 50 ng/ml. One subject transiently achieved a maximum bismuth concentration (Cmax) higher than 50 ng/ml (73 ng/ml) following multiple dosing of Pylera with omeprazole. The patient did not exhibit symptoms of neurotoxicity during the study. There is no clinical evidence to suggest that short-term exposure to Cmax concentrations above 50 ng/ml is associated with neurotoxicity.

The influence of renal and hepatic impairment on exposure to Pylera has not been evaluated, although the exposure to metronidazole and tetracycline hydrochloride has been studied (see sections 4.2, 4.3, 4.4 and 4.8).

5.3 Preclinical safety data

No non-clinical studies have been performed to evaluate the effect of the combined use of bismuth subcitrate potassium, tetracycline hydrochloride and metronidazole.

Non-clinical data, where available for colloidal bismuth subcitrate (colloidal bismuth subcitrate is similar to bismuth subcitrate potassium in terms of physicochemical, structural, biological (MIC *in vitro* study) and pharmacokinetic characteristics), reveal no specific hazard for humans based on studies of safety pharmacology, repeat-dose toxicity, genotoxicity and reproductive and developmental toxicity.

Non-clinical data, where available, for tetracycline hydrochloride reveal no specific hazard for humans based on studies of repeat-dose toxicity, genotoxicity, and carcinogenic potential.

Fertility was impaired in male rats (effects spermatozoa and testes). Results of animal studies indicate that tetracycline crosses the placenta, is found in foetal tissues, and can have toxic effects on the developing foetus (often related to retardation of

skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. Tetracycline is excreted in the milk of lactating rats.

Non-clinical data, where available, for metronidazole reveal no special hazard for humans based on studies of safety pharmacology, repeat-dose toxicity and genotoxicity. Metronidazole has been shown to be carcinogenic in mice and rats. Fertility was impaired in male mice and rats (effects on spermatozoa and testes). Metronidazole was not teratogenic in mice, rats or rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate (E572) Talc (E553b)

Lactose monohydrate

Capsule shell:

Titanium dioxide (E171) Gelatin

Printing ink:

Red iron oxide (E172) Shellac

Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

HDPE bottle with a child-resistant closure, rayon coil and desiccant (silica gel). Pack size of 120 capsules.

6.6 Special precautions for disposal

It is recommended that medicines should not be disposed of via wastewater or household waste. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Laboratoires Juvisé Pharmaceuticals

149 Boulevard Bataille De Stalingrad

69100 Villeurbanne

France

8 MARKETING AUTHORISATION NUMBER(S)

PL 43311/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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