EU RISK MANAGEMENT PLAN

Active substance(s) (INN or common name):	Erythromycin as Erythromycin Lactobionate
Pharmaco-therapeutic group (ATC Code):	ANTIBACTERIAL FOR SYSTEMIC USE (J01FA01)
Name of Marketing Authorisation Holder or Applicant:	PANPHARMA ZI. Du Clairay 35133 Luitré France
Number of medicinal products to which this RMP refers:	• 1
Product(s) concerned (brand name(s)):	ERYTHROMYCIN PANPHARMA 1 g, powder for solution for infusion

Data lock point for this RMP	06th February 2013	Version number	03
Date of final sign off	17-Mar-2014		

Summary of activities in the risk management plan by product

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

ERYTHROMYCIN PANPHARMA® is used to treat and prevent infections such as:
- Upper and lower respiratory tract infections;
- Eye, mouth or ear infections;
- Skin and soft tissue infections;
- Gastrointestinal infections;
- Prevention of infections in rheumatic fever;
- Other infections, such as: osteomyelitis (a bone infection), urethritis (inflammation of the urethra, a tube that carries urine from the body), gonorrhoea, syphilis (sexually transmitted diseases), endocarditis (inflammation of the inner layer of the heart), lymphogranuloma venerum (a sexually transmitted disease), diphtheria (an upper respiratory tract illness); prostatitis (inflammation of the prostate gland), scarlet fever.

- Incidence and prevalence : N/A
- Demographics of the target population – age, sex, race/ethnic origin : N/A
- Risk factors for the disease : N/A
- Main treatment options : N/A
- Mortality and morbidity (natural history) : N/A

VI.2.2 Summary of treatment benefits

ERYTHROMYCIN PANPHARMA® is an antibiotic that contains erythromycin (as erythromycin lactobionate). It is a type of antibiotic called macrolide which acts by preventing the growth and multiplication of bacteria.

ERYTHROMYCIN PANPHARMA® is used to treat of serious infections caused by bacteria in patients unable to swallow oral forms of ERYTHROMYCIN PANPHARMA® or in patients in whom the severtity of the infection requires high levels of erythromycin.
Once the acute phase of the infection is controlled, your doctor will replace the intravenous erythromycin with an oral form of erythromycin.

The medicine can only be obtained with a prescription.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Cardiac disorders including: • **Irregular heartbeat,** • **Heart beating forcefully or rapidly.** **(Cardiac Adverse Events)**	Patients treated with ERYTHROMYCIN PANPHARMA® have a greater risk of developing episodes of ventricular tachycardia (abnormal heart rhythms) associated with prolonged QT interval (alteration of the electrical activity of the heart) which may be fatal.	Yes, by monitoring for early symptoms. In addition, to avoid the risk of development of torsades de pointes arrhythmias (alteration of the electrical activity of the heart), is recommended to check electrolyte imbalance (increase or decrease of electrolytes in the blood), hepatic dysfunction (liver disorders), myocardial ischemia (reduced blood flow to the heart muscle), left ventricular dysfunction (cardiac disorders), idiopathic Q-T prolongation (alteration of the electrical activity of the heart) and concurrent antiarrhythmic therapy (medicine used for the treatment of abnormal heart rhythms). Specific information about these risks was included in the package leaflet.
Allergic reactions (i.e severe skin reactions, skin peeling, **Widespread skin rash, skin itchiness, redness of the skin with increase of blood flow, hives, skin eruptions,** **swelling of certain part of the body including face and neck) (Allergic reactions)**	Allergic reactions ranging from urticaria to allergic oedema/angioedema, anaphylaxis (swelling of certain part of the body including face and neck). Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome (severe skin reactions), and toxic epidermal necrolysis (skin peeling).	ERYTHROMYCIN PANPHARMA® must not be used in people who are hypersensitive (allergic) to erythromycin or to the macrolide class of antibiotics. The patient must be asked about his allergy history. Specific information about these risks was included in the package leaflet.
Inability of the kidney to perform normal function, inability of the liver to perform normal function, loss of hearing (Renal	Erythromycin is mainly excreted by the liver and caution should be exercised when using erythromycin in patients who have problems with the way their liver or kidney works because there is a greater risk of developing kidney disease or in patients concomitantly receiving agents potentially toxic for the liver.	Yes, careful calculation of the dose for the patient, particularly in elderly patient and take into account the way of the kidneys and liver work. In case of patients with acute liver disorder receive high doses of erythromycin, monitoring of

Risk	What is known	Preventability
impairment, hepatic impairment, hearing loss).	Elderly patients exhibit a greater risk of developing a kidney disease, cardiac disease, and of concomitant disease and other drug therapy . Elderly patients, particularly those with inability of the kidney to perform normal function or inability of the liver to perform normal function, may also be at increased risk for developing reversible hearing loss particularly in patients receiving high doses of erythromycin.	blood levels and dosage reduction will be required. The associated risk of hearing loss and early symptoms will be also closely monitored. Specific information about these risks was included in the package leaflet.
Overdose - related damage to the ear or hearing loss (Overdose - related ototoxicity or hearing loss)	Although this medication is not particularly toxic, an overdose could cause problems. The specific effects of an overdose with erythromycin would likely vary, depending on a number of factors, including the erythromycin dosage, the particular form of the medication, and whether it was taken with any other drugs or substances. An erythromycin overdose is likely to cause any of the usual side effects of the drug, such as diarrhea, nausea, vomiting and upset stomach. The ototoxicity (damage to the ear) and hearing loss that may accompany an overdose is usually temporary and typically goes away with time. Similarly, an overdose might cause an irregular heart rhythm, which should also improve once the medication is stopped. In addition, erythromycin affects the metabolism of many other drugs and can increase the level of such drugs in the bloodstream. Therefore, it is possible that an erythromycin overdose may cause toxic effects from the other drugs, particularly in people unaccustomed to taking this antibiotic.	Treatment involves supportive and symptomatic care, which consists of treating the symptoms that occur as a result of the overdose. Specific information about these risks was included in the package leaflet.
Liver disorders (Hepatic dysfunction)	In the presence of normal hepatic function, erythromycin is mainly excreted by the liver. Although the effect of liver disorders on the excretion of erythromycin is not known, caution should be exercised in administering the medicine in such cases, particularly in patients with acute liver disorder receiving high doses of erythromycin. Liver disorders including abnormal liver and gallbladder function detected by blood tests has been infrequently reported	Yes, caution should be exercised when using erythromycin in patients with liver disorders or in patients concomitantly receiving agents potentially toxic for the liver. In case of patients with acute liver disorder receive high doses of erythromycin, monitoring of blood levels and dosage reduction will be required.

Risk	What is known	Preventability
		Specific information about these risks was included in the package leaflet.
Inflammation of the colon with severe diarrhoea (Clostridium difficile-associated diarrhoea / Pseudomembranous colitis)	Practically all antibiotics, including erythromycin, are associated with inflammation of the colon with severe diarrhoea (clostridium difficile-associated diarrhoea (CDAD)) which can occur up to two months afterwards as light diarrhoea to lethally progressive colitis.	In case of inflammation of the colon with severe diarrhoea (CDAD), an end to treatment, depending on the indication, should be considered, and if necessary, appropriate treatment be initiated. Drugs, which inhibit peristalsis, (drug which slows of gastrointestinal transit time) are contraindicated in case of inflammation of the colon with severe diarrhoea (pseudomembranous colitis) occurs. Specific information about these risks was included in the package leaflet.
Vomiting (projectile non-bilious vomiting) or having troubles eating and weight loss in infants (Infantile Hypertrophic Pyloric Stenosis)	There have been reports of vomiting (projectile non-bilious vomiting) or having troubles eating and weight loss (Infantile Hypertrophic Pyloric Stenosis (IHPS)) occurring in infants following erythromycin therapy.	Yes, since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity, the benefit of erythromycin therapy needs to be carefully considered against the potential risk of developing vomiting (projectile non-bilious vomiting) or having troubles eating and weight loss (IHPS). A carreful monitoring for early symptoms must be exercised. Patients should be informed to contact their physician if vomiting or irritability occurs. Specific information about these risks was included in the package leaflet.
Swelling and redness along a vein which is	Side effects following the use of intravenous erythromycin are rare. Occasional swelling and redness along a vein	Yes, medicine, in dilute solution, must be given by continuous or slow intravenous (into a vein)

Risk	What is known	Preventability
extremely tender when touched (Venous irritation)	which is extremely tender when touched (venous irritation) has been encountered.	infusion over 60 minutes, in order to avoid pain and vessel trauma. Specific information about these risks was included in the package leaflet.
Interaction other medicines (Interaction with other medicinal products and other forms of interaction)	Drug interactions between erythromycin and other medicinal products were observed particularly with : warfarin and coumarin derivatives (used to thin the blood); ergotamine or dihydroergotamine (for migraine); penicillin, fluoroquinolones and clarithromycin (antibiotics used to treat certain infections);a ntifungal and anti-malarial medicines; pimozide (used in the treatment of psychiatric disorders); zopiclone (induces sleep); theophylline (helps breathing); lovastatin, simvastatin and atorvastatin (blood cholesterol lowering medicines); astemizole, terfenadine, ebastine, mizolastine (used to treat allergic reactions); some cytostatic medicines and vinblastine (used to treat cancer); digoxin (used to treat heart problems); carbamazepine (used to treat epilepsy and neuropathic pain); cisapride (used to treat gastroesophageal reflux disease), alfentanil, alprazolam, bromocriptine, cimetidine, quinidine, cyclosporine, cilostazol, clozapine, colchicine, disopyramide, felodipine, methylprednisolone, midazolam, omeprazole, phenytoin, ritonavir, sildenafil, sirolimus, tacrolimus, tadafanil, triazolam, valproic acid; vardenafil, verapamil, antiarrhythmic class Ia and III neuroleptics, tri- and trtracyclic antidepressants, methadone and budipine.	Yes, the concomitant administration of erythromycin with several of these medicinal products is contraindicated. With the other drugs that interact with erythromycin, particular care must be exercised when these medicinal products are administered concomitantly. In some cases, blood concentrations of drugs administrated concomitantly should be monitored closely in patients concurrently receiving erythromycin. Specific information about these risks was included in the package leaflet.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
None	Not applicable

Important missing information

Risk	What is known
Exposure during pregnancy	There was no evidence of teratogenicity (fetal abnormalities or deformities) or any other adverse effect on reproduction in female rats fed erythromycin base prior to and during mating, during gestation, and through weaning of two successive litters. There are, however, no adequate data in pregnant women. Because animal

Risk	What is known
	reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Erythromycin has been reported to cross the placenta and reach the unborn child. The effect of erythromycin on labor and delivery is unknown. [1] *References:* 1) Erythrocin lactobionate injection powder lyophilized for solution. Hospira, Inc. 2012. USA.
Effect on fertility	No data exists on the effect of erythromycin on fertility in human subjects. Animal studies showed that erythromycin has no teratogenic effects.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The proposed Summaries of Product Characteristics and the corresponding Package leaflets for ERYTHROMYCIN PANPHARMA® can be found in annex 2 of the RMP.

These risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

Risk minimisation measures: Irregular heartbeat, heart beating forcefully or rapidly (Cardiac events)
Objective and rationale Health Care Professionnal and patients to understand the risk of occurrence of cardiac events and the appropriate management of this risk.
• Summary description of main additional risk minimisation measures - Key points: - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take. These information were provided in the following sections: - "4.2 Posology and method of administration" - "4.3 Contraindications" - "4.4 Special warnings and precautions for use" - "4.5 Interaction with other medicinal products and other forms of interaction" - "4.8 Undesirable effects" - "4.9 Overdose". - The corresponding package leaflet is important tool for risk minimisation as they inform the patient about the symptoms of cardiac events and the importance of seeking medical help immediately. - Restricted medical prescription The medicinal product is used for the treatment of conditions which must be diagnosed in a

Risk minimisation measures: Irregular heartbeat, heart beating forcefully or rapidly (Cardiac events)
hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

Risk minimisation measures: Allergic reactions (i.e severe skin reactions, skin peeling, Widespread skin rash, skin itchiness, redness of the skin with increase of blood flow, hives, skin eruptions, swelling of certain part of the body including face and neck) (Allergic reactions)
Objective and rationale Health Care Professionnal and patients to understand the risk of occurrence of allergic reactions and the appropriate management of this risk.
• Summary description of main additional risk minimisation measures - Key points: - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take. These information were provided in the following sections: - "4.3 Contraindications", - "4.4 Special warnings and precautions for use", and - "4.8 Undesirable effects". - The corresponding package leaflet is important tool for risk minimisation as they inform the patient about the symptoms of allergic reactions and the importance of seeking medical help immediately. - Restricted medical prescription The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

Risk minimisation measures: **Inability of the kidney to perform normal function, inability of the liver to perform normal function, loss of hearing (Renal impairment, hepatic impairment, hearing loss).**
Objective and rationale Health Care Professionnal and patients to understand these risks and the appropriate management of these risks.
• Summary description of main additional risk minimisation measures - Key points: - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take. These information were provided in the following sections: - "4.2 Posology and method of administration", - "4.3 Contraindications", - "4.8 Undesirable effects", and - "4.9 Overdose". - The corresponding package leaflets is important tool for risk minimisation as they inform the patient about these risks and the importance of seeking medical help immediately. - Restricted medical prescription

Risk minimisation measures:
Inability of the kidney to perform normal function, inability of the liver to perform normal function, loss of hearing (Renal impairment, hepatic impairment, hearing loss).

The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

Risk minimisation measures: Overdose - related damage to the ear or hearing loss (Overdose - related ototoxicity or hearing loss)

Objective and rationale
Health Care Professionnal and patients to understand these risks and the appropriate management of these risks.

- Summary description of main additional risk minimisation measures
  - Key points:
  - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take.

    These information were provided in the following sections:
    - "4.2 Posology and method of administration",
    - "4.8 Undesirable effects", and
    - "4.9 Overdose".
  - The corresponding package leaflet is important tool for risk minimisation as they inform the patient about the symptoms of overdose, the associated risks and the importance of seeking medical help immediately.
  - Restricted medical prescription

    The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

Risk minimisation measures: Liver disorders (Hepatic dysfunction)

Objective and rationale
Health Care Professionnal and patients to understand these risks and the appropriate management of these risks.

- Summary description of main additional risk minimisation measures
  - Key points:
  - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take.

    These information were provided in the following sections:
    - "4.2 Posology and method of administration",
    - "4.3 Contraindications",
    - "4.8 Undesirable effects", and
    - "4.9 Overdose".
  - The corresponding package leaflet is important tool for risk minimisation as they inform the patient about the symptoms of hepatic dysfunction and the importance of seeking medical help immediately.

Risk minimisation measures: Liver disorders (Hepatic dysfunction)

- Restricted medical prescription

  The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

Risk minimisation measures: Inflammation of the colon with severe diarrhoea (Clostridium difficile-associated diarrhoea / Pseudomembranous colitis)

Objective and rationale

Health Care Professionnal and patients to understand these risks and the appropriate management of these risks.

- Summary description of main additional risk minimisation measures
  - Key points:
  - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take.

    These information were provided in the following section:
    - "4.4 Special warnings and precautions for use", and
    - "4.8 Undesirable effects".
  - The corresponding package leaflet is important tool for risk minimisation as they inform the patient about the symptoms of clostridium difficile-associated diarrhoea and pseudomembranous colitis and the importance of seeking medical help immediately.
  - Restricted medical prescription

    The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

Risk minimisation measures: Vomiting (projectile non-bilious vomiting) or having troubles eating and weight loss in infants (Infantile Hypertrophic Pyloric Stenosis)

Objective and rationale

Health Care Professionnal and patients to understand these risks and the appropriate management of these risks.

- Summary description of main additional risk minimisation measures
  - Key points:
  - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take.

    These information were provided in the following sections:
    - "4.4 Special warnings and precautions for use",
    - "4.6 Fertility, pregnancy and lactation", and
    - "4.8 Undesirable effects".
  - The corresponding package leaflets is important tool for risk minimisation as they inform the patient about the symptoms of infantile hypertrophic pyloric stenosis and the importance of seeking medical help immediately.
  - Restricted medical prescription

    The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although

Risk minimisation measures: Vomiting (projectile non-bilious vomiting) or having troubles eating and weight loss in infants (Infantile Hypertrophic Pyloric Stenosis)
administration and follow up may be carried out elsewhere.

Risk minimisation measures: Swelling and redness along a vein which is extremely tender when touched (Venous irritation)
Objective and rationale Health Care Professionnal and patients to understand these risks and the appropriate management of these risks.
• Summary description of main additional risk minimisation measures - Key points: - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take. These information were provided in the following sections: - "4.2 Posology and method of administration", - "4.8 Undesirable effects", and - "6.6 Special precautions for disposal and other handling". - The corresponding package leaflet is important tool for risk minimisation as they inform the patient about the symptoms of venous irritation and the importance of seeking medical help immediately. - Restricted medical prescription The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

Risk minimisation measure(s): Interaction other medicines (Interaction with other medicinal products and other forms of interaction)
Objective and rationale Health Care Professionnal and patients to understand these risks and the appropriate management of these risks.
- Key points: - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take. These information were provided in the following sections: - "4.3 Contraindications", - "4.4 Special warnings and precautions for use", and - "4.5 Interaction with other medicinal products and other forms of interaction". - The corresponding package leaflet is important tool for risk minimisation as they inform the patient about the risk of interaction with other medicinal products and the importance of seeking medical help immediately. - Restricted medical prescription The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

Risk minimisation measure(s): Use during pregnancy (Exposure during pregnancy)
Objective and rationale Health Care Professionnal and patients to understand these risks and the appropriate management of these risks.
• Summary description of main additional risk minimisation measures - Key points: - The summary of product characteristics is important tool for risk minimisation as they constitute an educational, controlled and standardised format for informing prescribing physician and pharmacist about the medicinal product, these risks and measure to take. These information were provided in the following section: - "4.6 Fertility, pregnancy and lactation" - The corresponding package leaflet is important tool for risk minimisation as they inform the patient about the risk of exposure during pregnancy and the importance of seeking medical help immediately. - Restricted medical prescription The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.