Part VI: Summary of the risk management plan

Summary of risk management plan for ERYTHROMYCINE PANPHARMA, powder for solution for infusion (ERYTHROMYCINE)

This is a summary of the risk management plan (RMP) for Erythromycine panpharma, powder for solution for infusion. The RMP details important risks of Erythromycine panpharma, powder for solution for infusion, how these risks can be minimised, and how more information will be obtained about Erythromycine panpharma, powder for solution for infusion's risks and uncertainties (missing information).

Erythromycine panpharma, powder for solution for infusion's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Erythromycine panpharma, powder for solution for infusion should be used.

I. The medicine and what it is used for

Erythromycine panpharma, powder for solution for infusion is authorised for treatment of appropriately diagnosed bacterial infections in adults and children caused by susceptible strains of organisms when oral administration is not possible or insufficient. It is also indicated for the treatment of infections in patients with hypersensitivity to beta-lactams or when beta-lactams are not appropriate for other reasons (see SmPC for the full indication).

It contains erythromycin as the active substance and it is given by intravenous infusion.

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

Important risks of Erythromycine panpharma, powder for solution for infusion, together with measures to minimise such risks and the proposed studies for learning more about Erythromycine panpharma, powder for solution for infusion'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 package leaflet 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 so 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 prescription) can help to minimise its risks.

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

If important information that may affect the safe use of Erythromycine panpharma, powder for solution for infusion is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Erythromycine panpharma, powder for solution for infusion are risks that need special risk management activities to further investigate or minimise 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 a link with the use of Erythromycine panpharma, powder for solution for infusion. 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);

List of important risks and missing information	
Important identified risks	- Long QT syndrome - Severe skin reactions - Hepatobiliary disorders - Pseudomembranous colitis - Infantile Hypertrophic Pyloric Stenosis (IHPS) - Superinfections
Important potential risks	- Exacerbation of myasthenia gravis - Cardiovascular malformations in newborns
Missing information	- None

II.B Summary of important risks

Long QT syndrome	
Evidence for linking the risk to the medicine	According to international literature post-marketing experience and SmPC, long QT Syndrome could occur when product is administered quickly, when product is administered concomitantly with other products (described in SmPC section 4.5). This is a risk deeply documented in the SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 4.9.
Risk factors and risk groups	Patients with underlying heart diseases, congenital long QT syndrome, metabolic derangement and patients treated concomitantly with medicinal products that may prolong the QT interval such as terfenadine, astemizole, cisapride, antiarrhymics class IA (quinidine, dysopyramide) and III, certains neuroleptics (pimozide), tri-and tetra cyclic antidepressants, arsenic trioxide, methadone, certain fluoroquinolones, imidazole antifungal and antimalarial such as IV pentamidine.
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC section 4.2 Posology and method of administration, - SmPC Section 4.3 Contraindications;

	- SmPC Section 4.4 Special warning and precautions of use; - SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions; - SmPC Section 4.8 Undesirable effects. - PIL Section 2 and section 4. **Additional risk minimisation measures:** Not applicable.

Severe skin reactions	
Evidence for linking the risk to the medicine	Severe, life-threatening allergic reactions may occur during the treatment with erythromycin such as serious skin conditions like urticarial, erythema multiform exudativum, Stevens-Johnson syndrome or toxic epidermal necrolysis. Stevens-Johnson syndrome typically involves the skin and the mucous membranes. Although several classification schemes have been reported, the simplest classification breaks the disease down as follows (French LE et al, 2006): - Stevens-Johnson syndrome: A minor form of toxic epidermal necrolysis, with less than 10% body surface area (BSA) detachment, - Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis: Detachment of 10-30% of the BSA, - Toxic epidermal necrolysis: Detachment of more than 30% of the BSA. Toxic epidermal necrolysis is a potentially life-threatening dermatologic disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis and/or death. Furthermore, mucous membrane involvement can result in gastrointestinal haemorrhage, respiratory failure, ocular abnormalities, and genitourinary complications. Erythema multiforme is usually mild (erythema multiforme minor) – with only a few spots, causing little trouble and clearing up quickly – but there is also a rare but much more severe type (erythema multiforme major/bullous erythema multiforme) that can be life threatening with involvement of the mucus membranes inside the mouth, in the genital area, and on the conjunctiva of the eyes.
Risk factors and risk groups	<u>Risk groups or risk factors (TEN):</u> - Patients over 40 years - Women - Patients with HIV (regarding the risk of TEN) <u>Risk groups or risk factors (erythema multiforme):</u>

Severe skin reactions	
	- Patients 20-40 years of age, Patients with herpes simplex virus (HSV), Epstein-Barr virus (EBV), and histoplasmosis.
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC Section 4.3 Contraindications, - SmPC Section 4.4 Special warnings and precautions for use, - SmPC Section 4.8 Undesirable effects. - PIL Section 2 and section 4. **Additional risk minimisation measures:** None.

Hepatobiliary disorders	
Evidence for linking the risk to the medicine	Most cases of erythromycin induced liver disease are mild and self-limiting; however, very rare instances of severe acute hepatic injury leading to acute liver failure and need for transplantation or death have been described. Furthermore, isolated examples of prolonged cholestasis with vanishing bile duct syndrome have been reported (NIDDK, 2018).
Risk factors and risk groups	- Patients with long term treatment (2-3 weeks) or repeat treatment, - Patients with pre-existing liver damage - Overdose of erythromycin
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC 4.8 Undesirable effects - SmPC4.9 Overdose - PIL Section 4 **Additional risk minimisation measures:** None.

Pseudomembranous colitis	
Evidence for linking the risk to the medicine	Potential complications of pseudomembranous colitis are septic shock and toxic megacolon (massive dilation of the colon) which can lead to colic perforation and require a colectomy. Furthermore, the most severe forms of the colitis of the antibiotic

Pseudomembranous colitis	
	treatment are due to Clostridium difficile and are associated with a not insignificant mortality.
Risk factors and risk groups	- Increasing age, especially over 65 years - Patients with a weakened immune system or using medicines that weaken the immune system (such as chemotherapy) - History of inflammatory bowel disease (ulcerative colitis and Crohn's disease, colorectal cancer) - History of pseudomembranous colitis - Undergoing intestinal surgery or recent surgery - Hospital stay or a nursing home (particularly sharing a hospital room with an infected patient, intensive care unit stays, and prolonged hospital stays) Concomitant treatment with medicinal products that inhibit peristalsis
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC 4.4 Special warnings and precautions for use, - SmPC 4.8 Undesirable effects. - PIL Section 4. **Additional risk minimisation measures:** None.

Infantile Hypertrophic Pyloric Stenosis (IHPS)	
Evidence for linking the risk to the medicine	IHPS is characterised by hypertrophy of the pylorus resulting in gastric outlet obstruction, leading to the infant presenting with projectile vomiting and severe dehydration (Murchison et al., 2016).
Risk factors and risk groups	Although genetics (Krogh et al., 2010) and male sex (McMahon B et al., 2010) have been identified as risk factors, the aetiology of IHPS is largely unknown. Several studies have identified a strong relationship between exposure to erythromycin and development of IHPS (Maheshwai N et al., 2007) —with some studies identifying an eight to tenfold increase in risk of developing IHPS when erythromycin was administered in the first 2 weeks of life (Mavromati T et al., 1995).
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC Section 4.4 Special warning and precautions of use; - SmPC Section 4.8 Undesirable effects. - PIL Section 2 and section 4. **Additional risk minimisation measures:**

Infantile Hypertrophic Pyloric Stenosis (IHPS)	
	None.

Superinfections	
Evidence for linking the risk to the medicine	A resistance to antibiotic treatments can lead to the development of multi-drug resistant bacteria, drug inefficacy and worsening of symptoms of diseases. Without effective antimicrobials for prevention and treatment of infections, medical procedures such as organ transplantation, cancer chemotherapy, diabetes management and major surgery (for example, caesarean sections or hip replacements) become very high risk (WHO, 2018).
Risk factors and risk groups	Superinfection may occur with prolonged use, giving rise to overgrowth of non-susceptible organisms.
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC 4.4 Special warnings and precautions for use - SmPC 4.8 Undesirable effects - SmPC 5.1 Pharmacodynamic properties - PIL Section 4. **Additional risk minimisation measures:** None.

Exacerbation of myasthenia gravis	
Evidence for linking the risk to the medicine	Myasthenia gravis is classified as a neuromuscular disorder that the abnormal weakness of certain muscles is the main clinical manifestation. This problem can be seen worldwide and is an important problem in clinical neurology. Myasthenia gravis is a disorder presenting with the weakness of muscle and it can be problematic for normal life of the patient. In the most severe case, the patient might have respiratory failure and there is a need for intubation. Mechanical ventilation may be required (Yasri S et al., 2017). The use of antibiotic in the patient with myasthenia gravis has to be carefully monitored (Eymard B, 2014). Bhattacharyya et al. (2014) noted that exacerbation of MG is an important antibiotic-induced neurotoxicity. The condition can be serious and fatal if there is a delayed diagnosis. Erythromycin can exacerbate the symptoms of myasthenia gravis which may result in life threatening weakness of respiratory muscles.

Exacerbation of myasthenia gravis	
Risk factors and risk groups	Patients with myasthenia gravis
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC 4.4 Special warnings and precaution for use - SmPC 4.8 Undesirable effects - PIL Section 2 and section 4. **Additional risk minimisation measures:** None.

Cardiovascular malformations in newborns	
Evidence for linking the risk to the medicine	There are no animal reproductive toxicology studies with erythromycin available, but studies with other macrolides, that similar to erythromycin are potent hERG-channels blockers, have shown embryonic death and malformations (including cardiovascular defects and cleft palate). Mechanistic studies have shown that substances blocking the hERG-channel cause cardiovascular defects and embryonic death by inducing arrhythmia in the foetus. Observational studies in people reported cardiovascular abnormalities, when pregnant women took drugs containing erythromycin during early pregnancy. However the risks associated with this phenomenon have not been clearly established.
Risk factors and risk groups	Foetus
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC section 4.6 Fertility, pregnancy and lactation - PIL Section 2. **Additional risk minimisation measures:** None.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Erythromycine Panpharma.

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

Not applicable.