RISK MANAGEMENT PLAN

For

MEROPENEM TRIHYDRATE

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Infection of the lungs (pneumonia): Pneumonia killed an estimated 935,000 (15%) children under the age of five in 2013 of all deaths. In Europe, death rates are higher in children up to the age of four and in adults aged 75. The death rates are highest in western Europe in elderly people aged 80 and over i.e. 279 deaths per 100000 people while in eastern Europe in infants aged 0 to 6 days i.e. 278 deaths per 100000.

Broncho-pulmonary infections in cystic fibrosis: The worldwide incidences varied from 1 per 377 live births in parts of England to 1 per 90,000 Asian live births in Hawaii. Review of 6750 deaths due to cystic fibrosis in England and Wales from 1959-2008 reported that female sex and low socioeconomic status are associated with poorer outcomes than male sex and high socioeconomic status.

Complicated urinary tract infections: They occur most frequently between the ages of 16 and 35 years, with 10% of women getting an infection yearly and 60% having an infection at some point in their lives. Urinary tract infections occur four times more frequently in females than males. Urinary tract infections may affect 10% of people during childhood.

Complicated infections in the abdomen: A study conducted in Europe between Jan-2012 to Jun-2012 in 996 females and 1156 males with an average age of 53.8 years, mentioned the death rate of 7.5.

Intra- and post-partum infections (Infections that you can catch during or after delivery): Approximately 1.2 million of the world's annual 3 million stillbirths (delivery of dead fetus) occur in the intrapartum period, and a further 717,000 of 3.1 million annual neonatal deaths are caused by intrapartum events.

Complicated skin and soft tissue infections (cSSTI): Several studies have shown that about 4.3%-10.5% of septic (infected) episodes are caused by SSTIs. In large database study on skin related conditions in the intensive care unit (ICU), only 0.4% of all ICU admissions had SSTIs, and about 60% of which were necrotizing fasciitis (a severe bacterial infection of the tissues that line and separate muscles, that causes extensive tissue death).

Acute bacterial meningitis (Acute bacterial infection of the brain (meningitis)): About 3,200 people get bacterial meningitis and associated septicaemia in the UK each year. The incidence of meningococcal disease naturally fluctuates over time. Yearly cases of meningococcal B disease have been steadily dropping since a peak in 2000.

Neutropenic patients with fever that is suspected to be due to bacterial infection: Febrile neutropenia accounts for 50% of deaths in patients receiving chemotherapy for solid tumours. It also accounts for 70% to 75% of deaths in patients receiving chemotherapy for acute leukemia (blood cancer). If not treated in the first 48 hours, mortality approaches 50%.

VI.2.2 Summary of treatment benefits

The results of one clinical study confirm that monotherapy with meropenem is well tolerated and provides superior efficacy in the treatment of ventilator-associated pneumonia. The result of another clinical study suggests that meropenem may be a carbapenem agent that is well tolerated and effective in the treatment of bacterial meningitis. Meropenem showed greater efficacy in febrile neutropenia, and greater efficacy in patients with nosocomial pneumonia. Meropenem proved to be a valuable drug in the treatment of cystic fibrosis patients with chronic pulmonary infection with multiresistant P. aeruginosa and B. cepacia and with hypersensitivity reactions to other β-lactam drugs. Meropenem is likely to be of greatest value as empiric monotherapy in the treatment of serious infections for those caused by multiply-resistant pathogens. Meropenem is associated with a reduced length of hospital stay and a shorter duration of therapy among patients with complicated intra-abdominal infections. There is evidence that prophylactic antibiotics (eg, meropenem) may reduce the risk of infection of genital tract by 66-75%. The prompt administration of antibiotics in first 48 hours of neutropenic fever has resulted in a response rate of up to 60% to 70% and has decreased death rate to 10%. For complicated skin and soft tissue infections, the meropenem group had overall 86% success rate compared to 83% in imipenem-cilastatin group.

VI.2.3 Unknowns relating to treatment benefits

Data on use of meropenem Accord in children between 3 months to 11 years with kidney impairment and children under 3 months of age, pregnant or breast-feeding women are not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Antibiotic associated inflammation which causes abdominal pain or diarrhoea (Antibiotic-associated colitis and pseudomembranous colitis)	Medicines like meropenem can cause inflammation (redness, swelling) of the colon (large intestine), causing severe diarrhoea (Pseudomembranous colitis). Diarrhoea is a common side effect with meropenem and may affect up to 1 in 10 people. Other possible side effects of unknown frequency inflammation of the bowel with diarrhoea.	Yes Talk to your doctor or nurse before using meropenem Accord if you have had severe diarrhoea after taking other antibiotics.
Liver toxicity (Hepatic toxicity)	It may cause liver toxicity like improper secretion of bile flow (cholestasis) and cell burst (cytolysis). It also commonly increases liver enzyme level.	Yes Talk to your doctor or nurse before using meropenem Accord if you have had health problems, such as liver problems. Inform your doctor or pharmacist about the medicines currently you are talking and use of

Risk	What is known	Preventability
		alcohol. Alcohol use may be decreased or stopped.
Fits (Convulsion) (Seizures)	Meropenem can cause a rare (may affect up to 1 in 1,000 people) side effects of Fits (Convulsion).	Yes If you had fits in past inform to your doctor or pharmacist. If you get this side effect, talk to your doctor or pharmacist. Inform your doctor or pharmacist about the medicines currently you are talking (especially medicines used to treat fits)
Serious Allergic reactions (Serious hypersensitivity reactions)	Meropenem may cause Severe allergic reactions. The signs may include a sudden onset of severe rash, itching or hives on the skin; swelling of the face, lips, tongue or other parts of the body; Shortness of breath, wheezing (whistling sound that is made during breathing) or trouble breathing.	Yes If you have a severe allergic reaction, stop having Meropenem Accord and see a doctor straight away. Do not use Meropenem Accord if • You are allergic to meropenem or any of the other ingredients of Meropenem Accord • If you are allergic (hypersensitive) to other antibiotics such as penicillins, cephalosporins, or

Risk	What is known	Preventability
		carbapenems as you may also be allergic to meropenem
Failure to antibiotics therapy due to bacterial resistance (Carbapenem resistance)	Bacterial resistance to meropenem may result from: (1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) reduced affinity of the target PBPs (3) increased expression of efflux pump components, and (4) production of beta-lactamases that can hydrolyse carbapenems.	The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.
Interaction with other medicine like valproic acid/sodium valporate/ valpromide (Interaction with valproic acid/sodium valproate/valpromide)	Meropenem Accord should not be used with sodium valproate (used to treat epilepsy) because it may decrease the effect of sodium valproate.	Yes Tell your doctor or nurse if you are taking medicine like valproic acid/sodium valporate/ valpromide.

Important potential risks

Risk	What is known
None	-

Missing information

Risk	**What is known**
Use during pregnancy and breast feeding (lactation)	There are no or limited amount of data from the use of meropenem in pregnant women and it is unknown whether meropenem is excreted in human milk. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. It is preferable to avoid the use of meropenem during pregnancy. Small amounts of meropenem have been reported to be excreted in human milk. Meropenem should not be used in breast-feeding women unless the potential benefit for the mother justifies the potential risk to the baby. Your doctor will decide whether you should use Meropenem Accord. It is important that you tell your doctor if you are breast-feeding or if you intend to breast-feed before receiving Meropenem Accord. Small amounts of this medicine may pass into the breast milk and it may affect the baby. Therefore, your doctor will decide whether you should use Meropenem Accord while breast-feeding.
Use in children from 3 months to 11 years with kidney problem (renal impairment)	There is no experience or data of use in children from 3 months to 11 years with kidney problem.
Use in children under 3 months of age	The safe and effective use of meropenem in children under 3 months of age has not been established and the dosage has not been identified.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) 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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable

Version	Date	Safety Concern	Comment
3.0	12-Sep-2017	No change in safety concern.	RMP has been updated as per revised SmPC/ PIL per Day-120 and Day-145 comments received from IE (RMS) health authority.
2.0	25-Jul-2016	• The important identified risk "Severe hypersensitivity reactions (e.g. anaphylactic reaction, severe skin reaction)" has been modified to "Serious hypersensitivity reactions". • New important identified risk "Carbapenem resistance" has	As per the Day 70 and Day 100 - assessment reports, the relevant safety sections and product labelling information of RMP have been updated.

Version	Date	Safety Concern	Comment
		been added. • One important identified risk "Interaction with oral anticoagulant agents" has been removed.	