VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

- Pneumonia

Every year about 5 million people die of acute respiratory infections. Among these, pneumonia (infection of lungs) represents the most frequent cause of death, admission to hospital and medical consultation. Several factors (age, underlying disease, environment) influence mortality, morbidity and

also microbial etiology. Pneumonia is an inflammation of the lung tissue and is commonly caused by an infection with a germ (bacterium or virus). There are different bacteria that are the most common causes of pneumonia.

Hospital acquired pneumonia:

Nosocomial, or hospital, acquired pneumonia (inflammation of the lungs) is an infection of lower respiratory tract that was not present on admission to the hospital. Usually, infections occurring 48-72 hours after admission are considered hospital acquired. Nosocomial pneumonia is the second most common nosocomial infection (after urinary tract infections) and accounts for 15–20% of the total. It is the most common cause of death among nosocomial infections and is the primary cause of death in intensive care units. It is one of the most common diagnoses made in medical and surgical intensive care units (ICUs) and it is common in patients undergoing mechanical ventilation (assisted or controlled ventilation using mechanical devices that cycle automatically to generate airway pressure). Nosocomial pneumonia also occurs in patients in the general hospital wards who are not receiving mechanical ventilation. 90% of these infections are bacterial.

Community acquired pneumonia (CAP):

CAP is an infection caused by microorganisms found in the community rather than in the hospital or long-term care facility. The infection begins outside the hospital or is diagnosed within 48 hours after admission to the hospital in a person who has not been in a long-term care facility before admission. CAP is a major health problem because is an important cause of mortality and morbidity worldwide. A number of microorganisms can give rise to CAP, caused frequently by a bacterial infection, rather than a virus. CAP usually results from inhalation or aspiration of pulmonary pathogenic organisms into a lung segment or lobe.

- Broncho-pulmonary infections in cystic fibrosis

Bronchopulmonary infection in cystic fibrosis (CF) patients is associated with chronic progressive lung disease and episodes of acute exacerbation. Infection is predominantly caused by bacteria, although infections with viruses, mycoplasma and fungi may play undervalued roles.

- Complicated urinary tract infections

Urinary tract infections (UTIs) are common in general practice, accounting for 1-3% of all consultations. Almost half of all women report at least one UTI sometime during their lifetime, and after an initial UTI, 20% to 30% of women experience a recurrence. UTIs occur much less frequently in men at all ages.

Patients of either sex are more likely to develop a UTI if there is an abnormality of the renal tract or if there has been recent instrumentation of the renal tract.

The diagnosis of UTI in young children is important as a marker for urinary tract abnormalities. Urine infection in children is common. It can cause various symptoms. A course of medicines called antibiotics will usually clear the infection quickly. In most cases, a child with a urine infection will

make a full recovery. Sometimes tests to check on the kidneys and/or bladder are advised after the infection has cleared.

A complicated UTI is an urinary infection occurring in a patient with a structural or functional abnormality of the genito-urinary tract e.g. obstructions of the ureter (narrowing of the urethra, enlarged prostate) or impaired voiding.

The infection is commonly just in the bladder (when it is called cystitis), but may travel higher up to affect one or both kidneys as well. A kidney infection can cause an unpleasant illness (pyelonephritis) which is sometimes serious. Treatment includes medicines called antibiotics and painkillers. If the kidney was previously healthy then the patient is likely to make a full recovery. Complications occur in some cases, such as kidney damage or blood infection (septicaemia).

- Complicated intra-abdominal infections

Intra-abdominal infection (infection of the abdomen) is the invasion of the cavity of the abdomen (the space bounded by the vertebrae, abdominal muscles, diaphragm, and pelvic floor) with organisms that have the potential to cause disease.

Peritonitis is a term used for a condition in which inflammation occurs in the peritoneum (a continuous transparent membrane which lines the abdominal cavity and covers the abdominal organs) itself rather than as a result of pathology arising in another organ.

Intra-abdominal sepsis is a term used for any intra-abdominal infection and encompasses both localized and generalized peritonitis, whereas abscesses are localized collections of infected fluid.

The number of patients affected by infection of the abdomen depends on the cause. 10-30% of patients with cirrhosis (a condition in which the liver does not function properly due to long-term damage) develop spontaneous bacterial peritonitis (SBP). Three studies of patients with perforated appendicitis found an incidence of abscess formation of 20% after surgery. Another study of patients undergoing surgical removal of the vermiform appendix found an incidence of localized and generalized peritonitis of 26.4% and 14.0% respectively.

- Intra- and post-partum infections

Postpartum infections (PPI) remain an important cause of maternal morbidity and mortality. A significantnumber of women (1% to 7%) develop postpartum infections. The most common cause of postpartum infection is endomyometritis, but infections of the breast, urinary tract, episiotomy, surgical wound, or respiratory tract may also occur. Multiple risk factors for PPI have been identified that relate to intrapartum events, coexisting lower genital tract infections, general infectious risks, and intraoperative risks.

- Complicated skin and soft tissue infections

Skin and soft tissue infections (SSTIs) are a diverse group of infections, with a range of presentations and microbiological causes. cSSTIs are the more difficult of this clinical condition, and hospitalization is common for patients with a cSSTI, which is treated by drainage of the affected area and with antibiotics (including meropenem). This condition is covering a range of clinical presentations such as infections far below the skin surface, a need for surgical intervention, the presence of systemic signs of

infection in the bloodstream, the presence of undesired result of complication, decreased number of white blood cells, inadequate blood supply to the tissue, death of a group of the cells, burns and bites. Staphylococcus aureus is the commonest cause of SSTI across all continents and meropenem is well-suited for the treatment of infections caused by this microrganism.

- Acute bacterial meningitis

Acute bacterial meningitis is rapidly developing inflammation of the layers of tissue that cover the brain and spinal cord (meninges) and of the fluid-filled space between the meninges (subarachnoid space) when it is caused by bacteria. Acute bacterial meningitis can develop in infants and children, particularly in geographic areas where children are not vaccinated. As people age, acute bacterial meningitis becomes more common.

- Neutropenia due to a bacterial infection

Neutropenia can be caused by infection with microorganisms. Conversely, neutropenia can lead to infection, typically from bacterial organisms. Bacteria, viruses, and parasites are all known causes. Regarding bacterial infection, bacterial sepsis (whole-body inflammatory response to an infection) or infection with Salmonella (typhoid) or brucella are most common.

VI.2.2 Summary of treatment benefits

Meropenem belongs to the group of medicines known as “broad-spectrum penicillin antibiotics”. It can kill many kinds of bacteria and is indicated as empirical therapy prior to the identification of causative organisms, or for disease caused by single or multiple susceptible bacteria in both adults and children with a broad range of serious infections. Meropenem has a broad spectrum of in vitro activity against Gram-positive and Gram-negative pathogens. Meropenem has also shown efficacy in paediatric and adult patients with bacterial meningitis, and with or without tobramycin in patients with cystic fibrosis experiencing acute pulmonary exacerbations. Meropenem is well tolerated and has the advantage of being suitable for administration as rapid or slow infusion into the vein (intravenous). Its low propensity for inducing seizures means that it is suitable for treating bacterial meningitis and is the only carbapenem approved in this indication. Thus, meropenem continues to be an important option for the empirical treatment of serious bacterial infections in hospitalized patients.

A search of the worldwide scientific literature confirmed that meropenem therapy is safe and generates bacteriological efficacy. Hence, it can be used for serious infectious diseases. In particular, meropenem is effective and well tolerated in critically ill patients, including new-born babies even with very low birth weight, infants and elderly people (Guler *et al*., 2009; Kobayashi *et al*. 2010; Chytra *et al*., 2012; Cohen-Wolkowiez *et al*., 2012; Padari *et al*., 2012).

In addition, meropenem is clinically effective and safe for the treatment of patients with a fever and low white blood count whose immune system is depressed (Erbey *et al*., 2010; Imajo *et al*., 2012), for the treatment of patients with pneumonia (Okimoto *et al.,* 2009; Tokuyasu *et al*., 2009) in critically ill patients, for patients with serious infenctious diseases (Wakisaka *et al*., 2015), as also in patients with severe neutropenia and fever (Ferdosian *et al.*, 2013; Wakisaka *et al.,* 2015; Sezgin *et al*., 2014).

VI.2.3 Unknowns relating to treatment benefits

Meropenem can be given to patients of all ages over the age of 3 months as well as to patients with liver and kidney disease, although a lower dose is required in younger children and in people with more severe kidney disease. There is nothing to suggest that meropenem works better or worse in any particular group of people.

There is insufficient information regarding the effectiveness in children less than 3 months. The safety and efficacy of meropenem in this population group have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regimen.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Serious allergic (hypersensitivity) reactions including: • Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), an idiosyncratic adverse drug reaction that affects the skin and various internal organs. • Severe skin reactions characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis with systemic reactions (Mucous membrane involvement can result in gastrointestinal hemorrhage, respiratory failure, ocular abnormalities, and genitourinary complications) called toxic epidermal necrolysis (TEN). • Stevens-Johnson syndrome a severe disorder affects the skin, mucous membranes and eyes.	As with all beta-lactam antibiotics (e.g. penicillins and cephalosporins), serious and occasionally fatal hypersensitivity reactions have been reported. Very occasionally, cases of extremely severe skin reactions known as Stevens-Johnson syndrome and toxic epidermal necrolysis has been reported among meropenem-treated patients. This condition can be life threatening (5% of patients die from it). With not known frequency cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome) have also been reported. TEN and DRESS syndrome most commonly manifests two to eight weeks after starting the offending medicine, in this case meropenem) with a mean onset of three weeks. Patients who have experienced allergic reactions to penicillins or other similar antibiotic may be allergic to meropenem as well.	It is not possible always to prevent such conditions. If you have any symptom of a serious allergic reaction, you should stop treatment immediately and inform your doctor or pharmacist. You should not take meropenem if you are allergic to meropenem or any of the other ingredients of meropenem or if you are allergic to other antibiotics such as penicillins, cephalosporins, or carbapenems as you may also be allergic to meropenem. Your doctor needs to know before you take this medicine. Tell your doctor if this happens to you. In case of experiencing Stevens-Johnson syndrome, the condition would be treated earlier by a patient watching out for early symptoms such as fever, sore throat and fatigue and by a doctor stopping meropenem immediately. Other symptoms may be ulcers in the mouth or genital region and redness of the eyes. Patients who have had TEN must be counselled regarding the likely causative medication or agent, and they must be advised to avoid these

Risk	What is known	Preventability
		medications and those of the same or similar classes in the future. Cross-reactivity may occur with agents that chemically resemble the causative agent. The condition would be treated earlier by a patient watching out for early symptoms (severe rash or blistering or peeling skin, which symptoms may be associated with a high fever and joint pains,) and by a doctor stopping meropenem immediately. DRESS Syndrome diagnosis can be difficult due to the variable presentation of the syndrome and is more often obtained by exclusion. Symptoms such as rash, fever, and organ involvement can be attributed to a wide range of other causes. Your doctor will look beyond the skin as the severity and extent of skin involvement does not always correlate with the extent of internal organ involvement. Patients who have had DRESS Syndrome must be counselled regarding the likely causative medication or agent, and they must be advised to avoid these medications and those of the same or similar classes in the future. Cross-reactivity may occur with agents that chemically resemble the causative agent. The condition would be treated earlier by a patient watching out for early symptoms (severe rash or blistering or peeling skin, which symptoms may be associated with a high fever and joint pains,) and by a doctor stopping meropenem immediately.
Liver dysfunction with reduction or stoppage of bile (the digestive fluid	The increase in blood levels of various liver enzymes consists a	It is not possible to prevent dysfunction of the liver but you

Risk	What is known	Preventability
produced by the liver) flow between the liver cells and the duodenum (the first segment of the small intestine) and destruction of cells by rupture or disintegration of the membrane and loss of cell contents	common possible side effect among meropenem-treated patients when given for up to 14 days .These elevations are usually transient, mild and asymptomatic; and rarely require dose adjustment. Meropenem has also been linked to rare cases of reduction or stoppage of bile flow between the liver cells and the duodenum that usually arises after 1 to 3 weeks of therapy.	should talk to your doctor or pharmacist immediately if you have any symptom that indicates liver damage, like nausea, vomiting, anorexia, having a pale colour (pallor), abdominal pain or if your laboratory test results are abnormal. Reducing the dose or stopping meropenem in accordance with your doctor instructions will help limit/reverse the condition of reduction or stoppage of bile flow. Therefore, hepatic function should be closely monitored during treatment with meropenem.
Decreased number of a particular type of white blood cells called neutrophils in the blood (neutropenia) or decreased number of granulocytes (a major class of white blood cells that includes neutrophils, basophils, and eosinophils) or decreased number of platelets in blood (thrombocytopenia or a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over (haemolytic anaemia)	Occasionally, there may be a decrease in the number of neutrophils or a decrease in the number of platelets, in the blood of patients under meropenem therapy.	It is not possible to prevent a decrease in the number of these cells. Your doctor may advise you to do blood tests from time to time in order to trace such changes, and by reducing the dose or stopping meropenem will help limit/reverse the rise.
Acute inflammatory disease of the colon manifested with diarrhoea caused by antibiotics (Pseudomembranous colitis)	Rarely, diarrhoea due to pseudomembranous colitis has been reported in patients on meropenem. The same condition occurs with practically all antibiotics and may range in severity from mild to life threatening.	Talk to your doctor or pharmacist immediately if you have any early symptoms like loose bowels. Your doctor may decide the discontinuation of therapy with meropenem and the administration of specific treatment for Clostridium difficile. Medicinal products that inhibit peristalsis should not be given.
Fits (Convulsions)	Convulsions have been infrequently reported when taking meropenem but it is not known for certain if these were caused by the meropenem.	It is not possible to prevent the first convulsion, but further convulsions may be prevented by doctor reducing the dose or stopping meropenem once the first convulsion has occurred.

RISK MANAGEMENT PLAN

Risk	What is known	Preventability
Use of meropenem and valproic acid (used to treat epilepsy) at the same time.	Meropenem should not be used because it may decrease the effect of sodium valproate. In particular, decreased blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid with carbapenem agents is not considered to be manageable and therefore should be avoided.	Tell your doctor or pharmacist if you are taking valproic acid/sodium valproate. Meropenem should not be used at the same time with valproic acid/sodium valproate, unless a doctor feels that the potential benefit justifies the potential risk. In every case, it should be used under the direct supervision of the physician.
Use of meropenem and anticoagulants (known also as "blood thinners") used to prevent the clotting of the blood, at the same time.	Interaction with medicines used to thin the blood may occur. They are taken by mouth. The doctor may check-up closely the effect of the anticoagulants. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient This risk can be reduced if patients tell their doctor or pharmacist if they are taking, have recently taken or might take such medication.	Tell your doctor or pharmacist if you are taking or have recently taken medicines used to prevent the clotting of the blood (anticoagulants), like warfarin. If you have any unexplained bleeding or bruising when taking anticoagulant, talk to your doctor or pharmacist immediately. Modification of the daily dose of anticoagulant may be needed.
Use of meropenem and Probenecid (a medicine used to treat gout) at the same time	Probenecid (a medicine used to treat gout) interfers with the removal of meropenem from the body in the urine, with the effect of increasing the blood levels of meropenem. As the levels of	Tell your doctor or pharmacist if you are taking probenecid. Caution is required if probenecid is co-administered with meropenem and it should be used under the direct supervision of the physician.

Risk	What is known	Preventability
	meropenem are adequate without probenecid it is not recommended that probenecid and meropenem be used at the same time.	
Resistance to penems of *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp*. across the European Union.	An increasing number of reports on penems resistance of microorganisms including *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp.*, has been published in recent years across Europe.	Within a healthcare setting, increases in species-specific (Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp.) carbapenem resistance should be monitored and sudden increases investigated to rule out an outbreak of resistant organisms or spurious test results.

Important potential risks

Risk	What is known
Kidney problems (Nephrotoxicity)	Changes in blood tests, including tests that show how well your kidneys are working may be observed during meropenem therapy.

Missing information

Risk	What is known
Effect on pregnancy and breast-feeding	**Pregnancy** The safety of meropenem in human pregnancy has not been established. Animal studies have not shown any adverse effect on the developing foetus. However, meropenem should not be used in pregnancy unless a doctor feels that the potential benefit justifies the potential risk to the foetus. In every case, it should be used under the direct supervision of the physician. **Breast feeding** It is unknown whether meropenem is excreted in human milk. Meropenem can be found at very low concentrations in animal breast milk. Therefore, meropenem should not be used by breast feeding women unless a doctor feels that the potential benefit justifies the potential risk to the baby. **Animal safety data** There was no evidence of congenital abnormality mutagenic in studies at the highest possible doses in rats and monkeys. There was an increased incidence of abortions at very high doses (500 mg/kg) in a preliminary study in monkeys.

Risk	What is known
Use in infants under 3 months	The safety and efficacy of meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regimen.
Use in children with kidney or liver dysfunction	There is no experience in children with kidney or liver dysfunction. In every case, it should be used under the direct supervision of the physician.
No data for driving and using machines	No studies on the effect on the ability to drive and use machines have been performed. <Meropenem> has been associated with headache and tingling or pricking skin (paraesthesiae). Any of these side effects could affect your ability to drive or operate machines. <Meropenem> may cause involuntary muscle movements which may cause the person's body to shake rapidly and uncontrollably (convulsions). This is usually accompanied with a loss of consciousness. Do not drive or use machines if you experience this side effect.

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

Further details about how to use Meropenem, the risks and recommendations for minimising them can be found in the leaflet supplied with the medicine. The measures in this document are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

There are no planned efficacy studies or further investigation of safety concerns.

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

Significant changes to the Risk Management Plan over time

This is the first RMP.