VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pneumonia

The description by Sir William Osler, “Pneumonia remains now, as then, the most serious disease with which physicians have to deal; serious because it attacks the old, the feeble persons who are not able to withstand the sudden sharp onset of the malady,” still stands the test of time. Over a century later, pneumonia remains a major cause of complications and death in the elderly. In 2005, the disease and influenza were the eighth-leading cause of death in the United States and the leading cause of infection-related death of all age-groups. An estimated 90% of deaths caused by these diseases occur among adults 65 years of age or older (Assaad et al., 2012).

Urinary tract infections

The urinary tract is the most common site of bacterial infections. Urinary tract infections in women require frequent and repeated use of drugs that kill bacteria, which can lead to resistant bacteria (Carraro-Eduardo and Gava, 2012).
Urinary tract infection is one of the most common bacterial infections seen at the family doctor´s practice. Infections of the urinary tract can present with various symptoms and signs and are particularly common among women, with an incidence of about 3-9% in young women and 20% in women aged more than 65 years (Medina-Bombardo and Jover-Palmer, 2011). Urinary tract infections can spread to the blood and cause bacteraemia (Beveridge et al., 2011).

Complicated intra-abdominal infections

Intra-abdominal infections represent a particular clinical challenge, as they differ from other types of infections in a number of aspects. The clinical spectrum of intra-abdominal infections is very broad, ranging from uncomplicated inflammation of the blind gut to generalised inflammation of the peritoneum (Blot et al., 2012).
Antimicrobial therapy plays an important role in the management of intra-abdominal infections, especially in patients who are treated in the intensive care unit and who require immediate antibiotic therapy. An insufficient or otherwise inadequate antimicrobial treatment is most strongly associated with unfavourable outcomes (Sartelli et al., 2012).
The main objective of antimicrobial therapy in the treatment of intra-abdominal infections is a prevention of a local spread or of a spread to the blood, and to reduce late complications. As for other infections, early administration of antibacterials is important (Blot et al., 2012).

Peritonitis associated with dialysis in patients on CAPD

Continuous ambulatory peritoneal dialysis (CAPD) has become the preferred method of home dialysis for patients with end-stage renal failure. An inflammation of the peritoneum (peritonitis) is a common and serious complication and requires prompt diagnosis and treatment. Peritonitis is the second commonest cause of death in patients undergoing CAPD (Al-Allak et al., 2009). Patients treated with peritoneal dialysis are exposed to a possible infection of the peritoneal cavity due to the non-natural communication of the peritoneal cavity with the exterior of the body through the dialysis catheter, and the repeated introduction of the dialysis fluid into the peritoneal cavity. The dialysis procedure itself is therefore a risk for peritoneal infection (Montenegro et al., 2007).

Bacterial meningitis

Meningitis refers to a group of infectious diseases of great social relevance, particularly taking into account the high fatality rates and sequelae that may occur when the membranes that envelop the brain are invaded by certain microorganisms. These diseases are included in the top 10 causes of death by infectious diseases worldwide, especially in developing countries (de Souza et al., 2012).
Although the incidence and rates of complications and death from acute meningitis have dramatically declined, probably as a result of vaccination and better antimicrobial and adjuvant therapy, the disease still has a high toll. From 10-20% of people who contract it in the United States still die of it. The organisms that cause community-acquired bacterial meningitis differ somewhat by geographic region and by age (Bhimraj, 2012).

Febrile neutropenia

Febrile neutropenia is still associated with many deaths, making timely and efficient empirical antibiotic therapy absolutely vital (Glasmacher et al., 2005).
Febrile neutropenia is defined as a reduced count of certain blood cells (neutrophil granulocytes) with fever, usually indicating infection, and is associated with complications, deaths, and costs. The direct risk of death associated with febrile neutropenia has been estimated as 9.5% in a study of 41.779 cancer patients hospitalised with febrile neutropenia (Cooper et al., 2011).
Febrile neutropenia presents a clinical challenge in which timely and appropriate antibiotic treatment is crucial. Antibiotic treatment in febrile neutropenia is becoming increasingly difficult due to a rising antibiotic resistance. Alternative dosing strategies, such as extended or continuous infusions of beta-lactam antibiotics, to maximise the likelihood of treatment success, have been developed (Abbott and Roberts, 2012).

Bacteraemia

Bacteraemia is a serious infection which is associated with many complications and death. Gram-negative bacteria have been documented as the most common cause of bacteraemia in many countries, but also infections caused by other bacteria represent an emerging problem in clinics, especially in patients with a depressed immune system. The bacteria, that can cause bacteraemia are very problematic because of their ubiquitous distributions in the environment and their antimicrobial resistance patterns (Rattanaumpawan et al., 2013).
In high-income countries, the rate of hospitalisation due to bacteraemia is around 77 to 92 per 100,000 people per year, and 13 to 19% die after 30 days. Bacteraemia is now the eleventh most frequent cause of death in the United States (Kanoksil et al., 2012).

VI.2.2 Summary of treatment benefits

- ***Pneumonia***
  198 patients with pneumonia were included in a study by Konstantinou et al. (2004) comparing treatment with cefepime and ceftazidime. All measurements were similar in the two treatment groups.
- ***Urinary tract infections***
  Sharifi et al. (1996) treated 118 patients suffering from urinary tract infections with cefepime. In complicated and uncomplicated urinary tract infections, 89% and 92% were cured, respectively. Eradication rates were 85% in both cases.
- ***Complicated intra-abdominal infections***
  Garbino et al. (2007) used either cefepime plus metronidazole (60 patients) or imipenem-cilastatin (61 patients) to treat intra-abdominal infections. Cefepime plus metronidazole treatment was successful in 87% of the patients and imipenem-

cilastatin in 72% of the patients. Microbiological eradication was established in both groups similarly.

- ***Peritonitis associated with dialysis in patients on CAPD***
  Wong et al. (2001) evaluated the efficacy of cefepime in the treatment of continuous ambulatory peritoneal dialysis (CAPD)-associated bacterial peritonitis in 39 patients, who received cefepime. Primary response rates and cure rates were 82% and 72%, respectively.
- ***Bacterial meningitis in children***
  Sáez-Llorenz and O'Ryan (2001) reported about 345 pediatric patients who suffered from central nervous system infections. The overall cure rate with cefepime among patients with microbiologically documented meningitis was 72%.
- ***Febrile neutropenia***
  Glasmacher et al. (2005) summarise several clinical practice guidelines, in which cefepime is recommended to be used as single treatment for initial therapy in neutropenic patients with fever of unknown origin and no particular risk factors.
- ***Bacteremia***
  Schrank et al. (1995) evaluated the efficacy and safety of cefepime in the treatment of 13 hospitalised patients with suspected gram-negative bacteremia. 11 of these 13 patients were clinically cured.

In all studies mentioned above, cefepime is described as an effective, safe, well-tolerated and cost-effective antibiotic for the treatment of nosocomial pneumonia, urinary tract infections, complicated intra-abdominal infections, peritonitis associated with dialysis in patients on CAPD, severe acute biliary tract infections, bacterial meningitis in children, febrile neutropenia and bacteremia. Cefepime has a broader spectrum of antibacterial activity than earlier generation cephalosporins and is more active against both Gram-positive and Gram-negative aerobic bacteria that cause several forms of infections.

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
Allergic reactions to any component of the medicinal product, to the cephalosporin class of antibacterials, to penicillins or other beta-lactam antibacterials or to L-arginine (Previous hypersensitivity to any component of the formulation, the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics (monobactams or	As with all beta-lactam antibacterials, serious and occasionally fatal allergic reactions have been reported. Patients must contact a doctor before beginning treatment and it should be checked whether the patient has had previous allergic reactions to cefepime, beta-lactams or other medicinal products. In 10 % of the cases there is a cross-allergy between penicillin and cephalosporin antibacterials.	Yes, by monitoring for early symptoms and by detection of hypersensitivity reactions in the patient´s history.

Risk	What is known	Preventability
carbapenems)or to the excipient L-arginine		
Overacidification or high levels of potassium in blood (Acidosis and hyperkalemia)	Due to its L-arginine content, this medicine must not be used in patients with high acidity in their blood. Caution is therefore advised in cases of high levels of potassium in the blood.	Yes, by carefully checking patient´s anamnesis and blood values.
Increased risk for neurotoxicity and severe adverse events in patients with impairmed kidney function, especially elderly patients	In patients with impaired kidney function, like a reduction of urine because of renal insufficiency (creatinine clearance $\leqslant$ 50 ml/min) or other conditions that may negatively affect kidney function, the dosage of cefepime should be adjusted to balance the slower rate of elimination by the kidneys. Because high and prolonged antibiotic concentrations in blood can occur from usual dosages in such patients, the maintenance dosage of cefepime should be reduced. Continued dosage should be determined by degree of kidney impairment, severity of infection, and susceptibility of the causal bacterium (see sections 4.2 - Posology and method of administration and 5.2 - Pharmacokinetic properties). During surveillance after launch, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, immobility and coma), convulsions, spasms (including nonconvulsive status epilepticus), and/or kidney failure (see section 4.8 - Undesirable effects). Most cases occurred in patients with kidney impairment who received doses of cefepime that exceeded recommendations. In general, symptoms of neurotoxicity resolved after stopping cefepime and/or after dialysis, however, some cases included a fatal outcome. **Elderly patients:** Of the more than 6400 adults treated with cefepime in clinical studies, 35 % were 65 years or older while 16% were 75 years or older. For elderly patients in clinical studies who received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in younger patients, unless the patients had kidney	Yes, by carefully monitoring the patient`s renal function and by adjusting dosage.

Risk	What is known	Preventability
	insufficiency. There was a moderate extension in elimination time and lower kidney clearance values compared to those seen in younger persons. Dosage adjustments are recommended if kidney function is compromised (see section 4.2 - Posology and administration and 5.2- Pharmacokinetic properties). Cefepime is known to be mainly excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired kidney function. Because elderly patients are more likely to have reduced kidney function, care should be taken in dose selection and renal function should be monitored (see sections 4.8 Undesirable effects and 5.2 - Pharmacokinetic properties). Serious adverse events, including reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, immobility, and coma), convulsions, spasms (including nonconvulsive status epilepticus), and/or kidney failure have occurred in elderly patients with kidney insufficiency given the usual dose of cefepime (see section 4.8 - Undesirable effects)	
Infection with microorganisms that are not susceptible to cefepime (overgrowth of non-susceptible microorganisms)	*Clostridium difficile*-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including cefepime, and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who suffer from diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterials. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. *difficile* may need to be discontinued. As with other antibacterials, use of cefepime may result in infection with organisms that are not susceptible to cefepime. Should such an infection occur during therapy, appropriate measures should be taken by the doctor.	Yes, by carefully monitoring the patient during and after treatment for adverse reactions concerning overgrowth of non-susceptible microorganisms.
Simultaneous intake of diuretics or antibacterials which belong to the	Kidney function should be monitored during simultaneous use of water tablets or special antibiotics.	Yes, by carefully checking patient´s anamnesis and

Risk	What is known	Preventability
group of aminoglycosides (medicinal products with the ending -mycin or -micin) (Concomitant use of loop diuretics or aminoglycosides)		blood values.
Allergic reactions to other medicinal products (Hypersensitivity reactions to other medicinal products)	Patients must contact a doctor before beginning treatment and it should be checked whether the patient has had previous allergic reactions to cefepime, beta-lactams or other medicinal products.	Yes, by monitoring for early symptoms and by detection of hypersensitivity reactions in the patient´s history.
Asthma or general susceptibility to allergic reactions (History of asthma or allergic diathesis)	Cefepime should be used with caution in patients with asthma or general susceptibility to allergic reactions. These patients must be carefully monitored during the first administration.	Yes, by monitoring for early symptoms and by detection of hypersensitivity reactions in the patient´s history.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
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Important missing information

Risk	What is known
Use of cefepime during pregnancy	Pregnancy studies in mice, rats, and rabbits showed no evidence of damage of the unborn child, however there are no adequate and well-controlled studies in pregnant women. Because animal pregnancy studies are not always predictive of human reaction, this drug should be used during pregnancy only if clearly needed.
Use of cefepime during lactation	Cefepime passes into human breast milk in very low concentrations. Caution should be used when cefepime is given to a nursing woman, then the infant should be monitored closely.
Use of cefepime in children below 2 months of age	Experience in infants younger than 2 months is limited. Dosage recommendations of 30 mg/kg every 12 or 8 hours were derived from pharmacokinetic data of children older than 2 months and are considered appropriate for infants from 1 to less than 2 months. <u>Dosage in patients with impaired kidney function</u>*:* *Infants from 1 month and children up to 12 years with a body weight of ≤ 40 kg*

Risk	What is known
	Data about the use of cefepime in infants younger than 2 months are not available. However, since all processes that cefepime is subjected to in the patient's body are comparable between children and adult patients, changes in dosage instructions are recommended for children with impaired kidney function similarly to those in adults. A dose of 50 mg/kg for patients between 2 months and 12 years and a dose of 30 mg/kg for infants aged 1 to 2 months is comparable to a dose of 2 g in adults including the same prolongation of dosing intervals as shown in the table.

VI.2.5 Summary of risk minimisation measures by safety concern

This medicine has no additional risk minimisation measures.

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.