

13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Septicemia

Septicemia (sepsis or infection of the blood) or presence of numerous actively dividing bacteria in the blood, leads to organ dysfunction. Septicemia is a serious illness and often fatal. It is the most common cause of death among critically ill patients in ICUs [Mayr FB, 2014]. Most studies in diseased population find sepsis to be more common in men than in women. Patients older than 65 years of age are particularly susceptible. The population-based number of cases of sepsis is estimated to be as high as 176 to 380 cases per 100,000 per year. The annual case count of sepsis in the EU has been estimated at 90.4 cases per 100,000 population. It is likely that there are as many as 20 million cases of sepsis annually worldwide, with a mortality rate of around 35%. An approximate of 20,000 deaths per day makes sepsis the second biggest killer after vascular disease (disease affecting blood vessels) [BMJ, 2015].

Skin and wound infections

Skin infections such as pyoderma (pus formation) and ectoparasitic infections (diseases that are caused by tiny parasitic bugs, such as lice or scabies) are common in developing countries, especially in tropical regions [Santos MML, 2010]. Surgical site infections are the second most common cause of hospital acquired infections [Elbur AI, 2012]. Most wound infections can be classified into two major categories: skin and soft tissue infections [Giacometti A, 2000]. Complicated Skin and soft tissue infections (wound infections) are among the most common infections treated in the hospitals accounting for 10% of admissions to infection units in the United States and the United Kingdom [Garau J, 2013]. *Staphylococcus aureus* bacteria can be found on the skin of 25–30% of the population; it is the most common cause of wound infections. MRSA is the most important hospital-acquired infection, causing, for example, problems related to surgery and prosthesis infections [WHO, 2016].

Diphtheria

Diphtheria is bacterial infection caused by *Corynebacterium diphtheriae*. The most common sites of diphtheria infection are pharynx, throat and tonsils. The overall death rate for diphtheria is 5%–10%, with higher death rates (up to 20%) among persons younger than 5 and older than 40 years of age. Diphtheria occurs worldwide, particularly in tropical countries. Human carriers are the reservoir for *C. diphtheriae* and are usually without any symptoms [CDC, 2015a]. During 2009–2013, 102 cases of diphtheria were reported in the EU/EEA with 55 cases of *C. diphtheria* [ECDC, 2015a]. In outbreaks, high percentages of children are found to be transient carriers, harboring the pathogen for brief period. Transmission is most often person-to-person spread from the respiratory tract. Rarely, transmission may occur from skin lesions or articles soiled with discharges from wounds of infected persons (fomites). Diphtheria most frequently occurs during winter and spring [CDC, 2015a].

Community acquired pneumonia

Community acquired pneumonia (CAP) [refers to pneumonia (an infection of lungs) acquired outside of hospitals or extended-care facilities] remains a major reason for admission to hospital and a common cause of death in developed countries. Most data have been obtained from hospitalized patients with CAP. CAP is associated with high rate of hospital admission, prolonged stay in hospital, and long period of inactivity of the patient. Approximately 2.6 to 13.4 adults per 1,000 suffer from CAP every year. Males are affected more than females and it is found more commonly in children and older people than young adults. Hospitalization rates of 22% to 51% and annual death rates of 0.1 to 0.7 per 1,000 have been reported [Almirall J, 2000]. Within Europe, CAP is the leading cause of death due to infection, with approximately 90% of deaths due to pneumonia occurring in people aged >65 years [Torres A, 2013].

Empyema

Pleural-thoracic empyema or empyema is a condition in which pus accumulates in the area between the lungs and the inner surface of the chest wall (pleural space), is a common and life threatening disease if not treated properly [Gupta P, 2015]. The cases of empyema seem to have been increasing both in children and adults worldwide in the past decades, mainly in healthy young adults and in older patients. In children, the most common microorganism that causes empyema continues to be *Streptococcus pneumoniae*. In adults, increases in the rate of empyema due to *Streptococcus milleri* group and *S. aureus* have been reported [Burgos J, 2013]. The disease is mainly seen in younger age group with maximum occurrence in less than 14 years of age is seen more commonly in young children and teenage population. Empyema occurs in <5% of pneumococcal pneumonia (lung infection) patients [Gupta P, 2015].

Erysipelas

Erysipelas or red skin is a serious skin infection that extends into superficial lymphatic tissue usually caused by *Streptococcus* bacteria. Isolated cases are the rule with erysipelas, although epidemics have been reported. The frequency of erysipelas declined throughout the mid-20th century, possibly due to antibiotic development, improved sanitation, and decreased capacity of the bacteria to cause the disease. However, an increasing frequency of the condition has been noted since the late 1980s. Erysipelas is somewhat more common in European countries. Approximately 80% cases of erysipelas occur on the legs rather than the face. Erysipelas infections affect people of all races. The condition has been reported to be more common in females but to occur at an earlier age in males. Cases of erysipelas have been reported in all age groups, but it does appear that infants, young children, and elderly patients are most commonly affected. It is most common in patients aged 60-80 years [Davis, 2014].

Bacterial endocarditis

Bacterial endocarditis is a rare bacterial infection of the inner lining of the heart, affecting about 3–10 per 100,000 people every year. Frequency and distribution of the disease in low-income countries is similar to that in high-income countries. Patients are usually young adults and infection is caused mainly by community-acquired, penicillin sensitive streptococci bacteria entering through the mouth. The average age of patients with infective endocarditis, which was in the mid-40s during the early 1980s, has increased to 70 years in June 2001. 25–30% cases of infective endocarditis are acquired from hospitals. Increasing use of long-term IV

lines and surgical procedures, use of various medical devices such as pacemaker (device for stimulating heart muscle to regulate its contraction) may lead to infective endocarditis. Infective endocarditis is rare in children, and the highest risk arises in children with several heart defects present at birth [Cahill TJ, 2015].

Peritonitis

Peritonitis is inflammation of the peritoneum, thin tissue that lines the inner wall of abdomen and covers most of the abdominal organs. Spontaneous bacterial peritonitis (SBP) is the infection of ascitic fluid (fluid that fills space between the lining of abdomen and organs) without an apparent source and is common bacterial infection in patients with liver damage and ascites (abnormal accumulation of fluid in abdominal cavity) [EASL, 2010]. SBP occurs in upto 30% of patients with cirrhosis and has an estimated in-hospital death rate of 20%. Between 25% and 65% of cirrhotic patients with digestive tract bleeding develop bacterial infection, including SBP. The recurrence rate of SBP at 1-year is approximately 70%, with a 1-year overall survival rate of 30% to 50% in patients who do not receive antibiotic prophylaxis [Liou IW, 2013]. Around 18% of the infection-related mortality in peritoneal dialysis patients is due to peritonitis [Akoh JA, 2012].

Meningitis

Meningitis is inflammation of membranes (meninges) surrounding brain and spinal cord which typically triggers symptoms such as headache, fever and a stiff neck.. Meningitis can result from many causes, both infectious and non-infectious. Over 1.2 million cases of bacterial meningitis are estimated to occur worldwide each year. Without treatment, the death rate can be as high as 70%, and one in 5 survivors of bacterial meningitis may be left with permanent sequelae including hearing loss, neurologic disability, or loss of a limb due to the blood infection. Meningitis due to *Streptococcus pneumoniae* bacteria occurs most commonly in the very young and the very old, with an estimated rate of 17 cases per 100,000 populations in children less than 5 years of age. The death rate for meningitis due to *S. pneumoniae* in children less than 5 years of age exceeds 73% in some parts of the world [CDC, 2012b].

Brain abscesses

Brain abscess is a pus-filled swelling in the brain caused by an infection with either bacteria or fungi, which is a rare and life-threatening condition. It can occur at any age, but most cases are reported in people aged 40 or younger and are more common in men than women. The chances of occurrence of brain abscess are higher in patients with HIV infection [NHS, 2016]. The case count is estimated at 0.3-1.3 per 100,000 people per year (non-HIV infected) [Beckham, 2012]. Recent studies from East Asia and Europe have reported marked variations in the outcome of brain abscess with mortality rates ranging from 6% to 35% and adverse outcome ranging from 10% to 58% [Helweg-Larsen J, 2012]. The current mortality of brain abscess patients is below 10% [Wiwanitkit S, 2012]. Brain abscesses are rare in developed countries, but are a significant problem in the developing world [Thomas, 2012].

Osteomyelitis

Osteomyelitis is an inflammatory process accompanied by bone destruction caused by an infecting microorganism that spread through blood from wound or infections somewhere else in the body [AAFP, 2011]. *Staphylococcus aureus* represents the most common isolated microorganism in most types of osteomyelitis, affecting 50% to 70% of cases [Prieto-Pérez L, 2014]. Osteomyelitis is a prevalent condition that affects males and females equally. It is usually common in children and adults after age of 50 years [NORD, 2005]. In children, it usually occurs in arms and legs. In adults, it usually affects feet, spine, or hips [AAFP, 2011]. Osteomyelitis affects 150 million people worldwide each year [The Osteomyelitis Center Of Central Florida]. The increasing age of general population has led to a rise in the prevalence of diabetes and poor blood circulation, both predisposing and complicating osteomyelitis, which if not managed, may result in amputation, sepsis, or death [Prieto-Pérez L, 2014].

Fusobacteria

Fusobacteria are a rare cause of serious human disease with common infecting species being *F. nucleatum* and *F. necrophorum* [Afra K, 2013]. Fusobacteria dwell in the oral, digestive tract, upper respiratory and genito-urinary tract as part of the normal flora. *F. nucleatum* infections are associated with increased morbidity and mortality. Because of the association with upper respiratory tract flora, they are frequently isolated from lung infections, [Shah C, 2015]. Fusobacteria affect young, healthy adults. In addition *F. nucleatum* also affects older individuals having co-morbidities like undergoing dialysis or underlying cancer. A study from Finland reported an annual new occurrence of Fusobacterium bacteremia of 0.55/100,000. The relative frequency of the 2 common species was equal (0.22 and 0.23/1000/ annum). Similarly, a study on *F. necrophorum* bacteremia in Denmark showed a new occurrence of 0.38/100,000. Mortality is low but occurs primarily in patients with *F. nucleatum*, likely due to associated co-morbidities [Afra K, 2013].

Anthrax

Anthrax is a serious infectious disease that can be transmitted from animals (sheep, cattle) to people, caused by *Bacillus anthracis* (a type of bacteria). The humans are affected through skin, digestive tract, or respiratory routes. Globally every year 2000 to 20,000 human anthrax cases were noted. 2000 cases were reported worldwide in 1980, mostly anthrax of skin from persons involved in industrial occupations related to processing of animal parts and products like meat packing, bone meal processing, tanning (conversion of animal skin) of leather and sorting (separation) of hair wool. Anthrax is still an important endemic disease (disease found in certain geographical region) of public health importance in several countries of Asia, Africa and Europe [Goel AK, 2015]. In 2012, overall 20 irregular cases of anthrax were recorded in 29 EU and EEA countries which were observed mainly in 15-64 year age group [ECDC, 2014].

Tetanus

Tetanus is an infection caused by *Clostridium tetani* bacteria present in soil and animal gut. Mode of transmission is through an infected wound or cut that takes the bacteria into the body. It affects all age groups but is common and serious in newborn and mothers when they were not protected by tetanus vaccine. According to World Health Organization (WHO; 2013), 49,000 newborn children died due to neonatal tetanus. In 2014 there were 11,367 cases of tetanus reported to the WHO [WHO, 2015]. The occurrence of tetanus was found to be very low (0.03 cases per 100,000 populations) in EU/EEA countries. According to the tetanus surveillance data by 26 EU/EEA countries in 2012, 123 tetanus cases were recorded in 15 EU/EEA countries, highest rate in Italy (0.09 per 100,000). The most affected group was the elderly (80%) and females (62%) of the reported cases [ECDC, 2014].

Gas gangrene

Gas gangrene is mostly caused by *Clostridium perfringens* bacteria. The bacteria can be found anywhere. They grow inside the body and produce gas and harmful substances (toxins) that damage various parts of the body [NIH]. The *Clostridium* species (type of bacteria) are the principal causes of trauma-associated gas gangrene and there is an increase in times of war, hurricanes, earthquakes and other mass casualty conditions [Stevens DL, 2012]. Civilian cases of gas gangrene are more common, with approximately 3,000 cases per year. Gas gangrene can be classified as posttraumatic, postoperative, or spontaneous. Posttraumatic gas gangrene accounts for 60% of all cases; most cases involve automobile collisions [Hoi H, 2015a]. In European theaters the occurrence of gas gangrene was higher than in desert operations because of higher contamination with *C. perfringens* [Num SM, 2014].

Listeriosis

Listeriosis is an uncommon but severe disease in Europe, caused by *Listeria monocytogenes* bacteria [ECDC, 2014]. The disease spreads through contaminated food and the bacteria's ability to persist and multiply in the food environment makes *L. monocytogenes* especially difficult to control. Listeriosis mainly occurs in particular at-risk groups: pregnant women, elderly people, unborn babies, and newborns and can lead to severe illnesses, including severe sepsis, meningitis or encephalitis of brain, causing lifelong consequences and even death in immune-compromised persons. In high-income countries, low number of cases of listeriosis with high death rate has been reported [Maertens de Noordhout C, 2014]. Overall, 1676 confirmed cases of listeriosis were reported by 28 EU and EEA countries in 2012 with an overall case rate of 0.35 per 100,000 populations. The highest number of listeriosis cases were observed in Finland (1.13 per 100,000) followed by Denmark with 0.90 per 100 000 inhabitants [ECDC, 2014].

Pasteurellosis

Pasteurellosis infection to humans was caused by *P. multocida* bacterial species and spread to humans through animal bites, scratches, licks on skin abrasions or contact with secretions derived from pets. Over the past 30 years, 20-30 human deaths due to pasteurellosis occur annually worldwide and the rate appears to be rising. *P. multocida* is the *Pasteurella* species most commonly found in humans, especially in severe disease cases [Wilson BA, 2013]. Infants

and individuals with less immunity are at higher risk of getting affected and 50% of cases in Europe and America are infected bites or scratches from animals, usually cats and dogs [PHAC, 2011]. In 2014, there were 173 laboratory reports of *Pasteurella*, of which 128 (74%) were associated with wound infections, of those, 62% were associated with dog or cat bites. *Pasteurella* species can also cause meningitis, eye and respiratory infections (related to lungs) [HPS weekly report, 2015].

Rat bite fever

Rat bite fever is a disease spread by animal to humans, caused by *Streptobacillus moniliformis* and *Spirillum minus* bacteria, due to bite of a wild or laboratory rat. *S moniliformis* is common in North America, while *S minus* infection is common in Asia. The youngest reported case was a 2 month old baby and oldest being an 87 year old man [Elliot SP, 2007]. Approximately 1 in 10 bites can cause infection [Adam JK, 2014]. Risk of rat bite fever is common in people who live in rat-infested buildings, have rats as pets or work with rats in laboratories or pet store. The common route of disease transmission is through bites or scratches from infected rodents (such as rats, mice, and gerbils), intake of food or drink contaminated with the bacteria [CDC, 2015b]. The symptoms include fever, rash and polyarthritis and the disease has a reported mortality of 7%–13% if untreated [McKee G, 2013].

Actinomycosis

Actinomycosis is a progressive *Actinomyces spp* bacterial infection which can cause disease only in the setting of antecedent tissue injury (as a result of a dental injury, a surgery or trauma) and is characterized by abscess formation, tissue fibrosis, and draining sinuses [Smego RA and Foglia G, 1998]. Common clinical forms are cervicofacial (ie, lumpy jaw), thoracic, and abdominal. Actinomycosis affects all ages, majorly young to middle-aged adults. It is spread worldwide, with higher rates observed in low socioeconomic status and poor dental hygiene [Moniruddin ABM, 2010]. The highest risk for actinomycosis is reported to be in fourth and fifth decades of life. Males are more affected than women, with 3:1 ratio [Valour F, 2014]. The number of cases of all forms of actinomycosis has declined in recent years, especially in developed countries as a result of better oral hygiene and susceptibility to broad range of antibiotics [Acevedo F, 2008].

Gonorrhoea

Gonorrhoea is a sexually transmitted bacterial infection by Gonococci that can affect genital, rectal, pharyngeal, or extragenital regions [Fuchs W, 2014]. It is the second most common disease in the United Kingdom, with nearly 29,000 diagnoses in 2012 and commonly seen in black ethnic origin [Hughes G, 2015]. In 2013, the total number of new cases of gonorrhoea diagnosed in genitourinary medicine clinics in England was 29,291. The highest rates of gonorrhoea are amongst the young [ECDC, Factsheet]. People with history of gonorrhoea or any other sexually transmitted infections, who have multiple sexual partners; who don't use condoms; whose partners are infected, young people, under the age of 25; men who have sex with men; and commercial sex workers are at risk [CDC Factsheet]. In about 50% of women, gonorrhoea remains asymptomatic. Men with genital gonorrhoea typically develop a highly purulent discharge 2–6 days after infection [Fuchs W, 2014].

Syphilis

Syphilis is a bacterial infection caused by *Treponema pallidum* [Fuchs W, 2014]. The infection can be congenital (transmitted from mother to child in utero) or acquired (through sex or blood transfusion) [WHO, 2003]. Each year an estimated number of 5.6 million cases of syphilis are reported worldwide [WHO, Factsheet]. During 2014, there were 63,450 reported new cases of syphilis, 19.9 were of primary and secondary syphilis, the earliest and most transmissible stages of syphilis [CDC Factsheetb]. If untreated, tertiary stage syphilis might develop that result in multi-organ involvement [ECDC]. In 2014, 24,541 syphilis cases were reported in 29 EU/EEA Member States, an overall rate of 5.1 per 100,000 population and rates were 6 times higher in men than in women. The majority of cases were reported in people older than 25 years, with young people between 15 and 24 years of age accounting for only 13% of cases [ECDC, 2015b].

Lyme borreliosis

Lyme disease (*Lyme borreliosis*), is caused by *Borrelia burgdorferi* bacteria and transmitted to humans through the bite of infected ticks [CDC Factsheetc]. *Borrelia* can affect several tissues with the predominant symptom being a red skin rash (erythema migrans) that occurs in about 60–90% of cases within 2–30 days of the tick bite. Lyme disease occurs in rural areas of Asia, north-western, central and eastern Europe, and the United States of America [WHO]. It is a common disease in Europe, more than 360,000 cases having been reported over the last two decades with Central Europe being the region with the highest occurrence of LB. Ticks become infected when they feed on small mammals (such as rodents) and certain birds that carry the bacterium in their blood. If left untreated, a disseminated infection affecting the nervous system (10% of cases), the joints, the skin and/or the heart (rare) may follow within days or weeks [WHO].

Fusospirochetosis

Fusospirochetosis, also known as necrotizing ulcerative gingivitis, trench mouth or Vincent's infection, is a very painful, stinking, sore disease that occurs most often in persons under severe stress with no or very poor oral hygiene. [Brook I, 2008]. Fusospirochetosis has been reported in closed communities such as in young recruits away from home and in new surroundings. Risk factors include crowding, physical fatigue, increased stress, low socioeconomic status, and failure of host defense mechanisms [S Melnick et al, 1988].

13.2.2 Part VI.2.2 Summary of treatment benefits

Penicillin G is used to treat a wide variety of bacterial infections, including pneumococcal infections, streptococcal infections, staphylococcal infections, diphtheria, meningitis, clostridial infections and anthrax. According to the Centers for Disease Control and Prevention (CDC), Penicillin G is the treatment of choice for congenital syphilis, neurosyphilis and prophylaxis of intrapartum group B streptococcus [Medical News, 2009]. Penicillin G Sodium is generally used in patients who cannot tolerate Penicillin G Potassium (eg, patients with kidney dysfunction) [CDC, 1994].

The use of penicillin in pregnant women with syphilis significantly reduces the risk of syphilis present at birth, death of newborns, stillbirth and preterm delivery (birth of baby before 37 completed weeks of gestation) [Galvao TF, 2013].

Intravenous penicillin is used in the treatment of severe leptospirosis (an infectious bacterial disease occurring in rodents, dogs, and other mammals, which can be transmitted to humans) [Panaphut T, 2003].

Penicillin G is used in the treatment of streptococcal arthritis (joint infection) and several types of osteomyelitis (bone infection)

High dose penicillin G in combination with metronidazole is used in the treatment of brain abscess (pus-filled swelling in the brain).

Penicillins are often used for prophylaxis of infective endocarditis in certain at-risk patients (eg, prosthetic valve in place or congenital heart anomaly) undergoing dental procedures/surgery, or minor gastrointestinal or genitourinary procedures. The prophylaxis is believed to treat the bacteremia that occurs during these procedures which could cause endocarditis.

Intravenous penicillin G is used in the treatment of CAP and nosocomial (hospital acquired) pneumonia. Penicillin G intravenously is the treatment of choice for actinomycosis (infectious bacterial disease) [Preston SL and Drusano M, 2014].

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There are no data available on the effect on fertility of penicillin G sodium.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-5 Important identified risks

Risk	What is known	Preventability
A reaction described in the treatment of syphilis (a sexually transmitted infection) and caused by the release of toxin-like substances when large numbers of <i>Treponema pallidum</i> (type of bacteria) are killed by antibiotics (Jarisch-Herxheimer reaction)	When treating certain infectious diseases like syphilis, meningitis (infection involving inflammation of protective membranes of the brain) and Lyme disease or borreliosis, a bodily reaction to the bacterial toxins may occur, which lasts up to several days (Jarisch-Herxheimer reaction). Typical symptoms are sudden fever (sometimes with chills), by skin redness, headache, painful muscles and joints or tiredness.	If any of the symptoms are experienced by the patient, doctor or pharmacist should be consulted. The doctor will help patients to relieve these temporary symptoms. In meningitis, due to Jarisch-Herxheimer reactions, not more than 20 - 30 MIU/day should be administered in adults and not more than 12 MIU/day in children. Administration of the first dose should be protracted for very severe clinical forms - initially 1/4 of the individual single dose - and given slowly under very strict surveillance.

Risk	What is known	Preventability
<p>Allergic reactions including life threatening reactions to the drug and other drugs of same class (Hypersensitivity including severe immediate hypersensitivity reaction to penicillin G, other penicillins, to another beta-lactam agent or to any of the excipients)</p>	<p>Allergic reactions like nettle rash with or without itching (urticaria); swelling of the skin and mucous membranes, especially in the facial region, mouth, throat and larynx (angioedema); severe skin reactions (erythema multiforme, exfoliative dermatitis); fever; joint pain; severe hypersensitivity reactions (asthma, skin bleeding, gastrointestinal disorders) occur uncommonly with Penicillin G Sodium.</p> <p>The frequency of hypersensitivity reactions such as fever, lymph node swelling, local redness at the injection site, itching was not known.</p> <p>A possible cross-allergic reaction that occurs when the components of drugs are similar should be considered in patients with hypersensitivity to cephalosporin.</p> <p>Due to the occurrence of possible serious side effects (eg, anaphylactic shock with collapse and anaphylactoid reactions), a hypersensitivity test should be carried out prior to treatment.</p>	<p>In Lyme borreliosis patients, adults, 20 - 30 MIU/day intravenously in 2 - 3 doses over 14 days and in children, 0.5 MIU/kg/day intravenously in 2 - 3 doses over 14 days should be administered.</p> <p>If a patient is allergic (hypersensitive) to penicillin G, other penicillins or any of the other ingredients of this medicine, or if the patient has ever been treated with a penicillin before and hypersensitivity reactions occurred (eg, skin rash, itching, fever, shortness of breath, drop in blood pressure), in this case, as there is a risk of life-threatening anaphylactic shock, Penicillin G Sodium must not be used.</p> <p>If the patient has a history of a severe immediate hypersensitivity reaction (eg, anaphylaxis) to another beta-lactam agent (eg, cephalosporin, carbapenem or monobactam) then penicillin G sodium should not be taken.</p> <p>If the patient has ever experienced signs of intolerance (lack of tolerance to the drug resulting in adverse effects) after using other antibiotics (eg, cephalosporins), then doctor or pharmacist should be consulted before taking the medicine as in this case, the doctor will decide whether penicillin G sodium may be used. Before the start of treatment, a hypersensitivity test should therefore be carried out.</p>

Risk	What is known	Preventability
		<p data-bbox="1059 300 1437 479">If patients are prone to an allergy or allergic asthma or hay fever, the doctor or pharmacist should be informed as there is increased risk of allergic reactions.</p> <p data-bbox="1059 524 1437 763">If the patient has glandular fever (mononucleosis) or is suffering from acute lymphatic leukemia (a type of blood cancer), the doctor or pharmacist should be informed as there is increased risk of skin reactions.</p> <p data-bbox="1059 808 1437 1021">If the patients are currently suffering from any fungal skin disease (dermatomycoses), the doctor or pharmacist should be informed as they are at increased risk of developing allergy-like reactions.</p> <p data-bbox="1059 1066 1437 1211">Severe local reactions may occur in infants upon intramuscular administration. Wherever possible, intravenous therapy should be performed.</p> <p data-bbox="1059 1256 1437 1435">The preparation of penicillin G sodium should be used immediately after the dissolution process to prevent hypersensitivity reactions by degradation products.</p> <p data-bbox="1059 1480 1437 1933">Prior to treatment, a hypersensitivity test should be carried out. Patients should be informed about the possible occurrence of a hypersensitivity reaction. Particular caution is required in patients with allergic diathesis (diathesis is an unusual constitutional susceptibility or predisposition to a particular disorder or disease) or bronchial asthma. After administering the medication, patients should be observed for 30 minutes and an</p>

Risk	What is known	Preventability
		adrenaline solution should be ready for injection in the event of an emergency. If an allergic reaction occurs, treatment must be discontinued and, if necessary, symptomatic treatment instituted.
Antibiotic associated inflammation of the colon (Antibiotic associated pseudomembranous colitis)	If the patient experiences severe, persistent diarrhea (loose motion), antibiotic-associated pseudomembranous colitis should be considered, which is uncommonly noted. Symptoms of this are bloody/mucous, watery diarrhea; dull, diffuse to colicky abdominal pain; fever or, occasionally, a constant and painful need to pass stools which may be life-threatening.	The doctor should be informed immediately. In such cases, Penicillin G Sodium should be stopped immediately and the doctor will start appropriate therapy according to patient pathogen detection test.
Electrolyte disturbances	Electrolyte imbalance may occur if administration is too rapid in rare cases.	<p>If the patient is suffering from severe electrolyte disorders (eg, sodium, calcium, potassium, chloride), the doctor should monitor patient intake of electrolytes, especially potassium intake.</p> <p>Penicillin G sodium should be administered slowly due to possible electrolyte disturbances when administering more than 10 MIU.</p> <p>In prolonged treatment (more than 5 days) with high penicillin doses, monitoring of the electrolyte balance is recommended.</p>
Drug interaction with medicine used to treat gout, a type of arthritis (Drug interaction with probenecid)	<p>The administration of probenecid, can lead to higher blood levels of penicillin G and increase the time that it remains within the body.</p> <p>Co-administration of probenecid along with penicillin G sodium reduces the entry of penicillin into brain tissue.</p>	The doctor or pharmacist should be informed if the patient is taking/using, has recently taken/used or might take/use probenecid before taking penicillin G sodium.

Risk	What is known	Preventability
Drug interaction with medicine used to treat heart failure (Drug interaction with digoxin)	If the digoxin given at the same time as penicillin G sodium, the heartbeat may become slower (bradycardia)	The doctor or pharmacist should be informed if the patient is taking/using, has recently taken/used or might take/use digoxin before taking penicillin G sodium.
Drug interaction with chemotherapy agent used in cancer treatment (Drug interaction with methotrexate)	When methotrexate, a medicine used in chemotherapy, is taken at the same time as penicillin G sodium, can lead to increased methotrexate toxicity as the excretion of methotrexate will be reduced.	The doctor or pharmacist should be informed if the patient is taking/using, has recently taken/used or might take/use methotrexate before taking penicillin G sodium. Combined use of methotrexate and penicillin must be avoided wherever possible. If combined use cannot be avoided, a reduction in the methotrexate dose should be considered and methotrexate serum levels should be monitored. The patient should be monitored for possible additional side effects of methotrexate, including leukopenia, thrombocytopenia and pus accumulation under the skin.

Table 13-6 Important potential risks

Risk	What is known
Skin conditions with blistering (Pemphigoid)	The frequency of pemphigoid is not known. Pemphigoid is a chronic auto-immune disease, characterized by blistering skin and mucosal membrane, which can occur with Penicillin G Sodium. Treatment must be discontinued if the patient experiences a pemphigoid. The patient should be treated with corticosteroids.

Drug interactions with blood thinners (Drug interaction with oral anticoagulants)	<p>Oral anticoagulants and penicillin antibiotics have been used extensively in practice without interactions. However, in the literature, there have been reports of an increased number of patients who experienced a bleeding event when they were prescribed acenocoumarol or warfarin at the same time as penicillin.</p> <p>When oral anticoagulants, drugs used to thin blood, is taken at the same time as Penicillin G Sodium, prolongation of the bleeding time and prothrombin time may occur. Caution should be exercised when anticoagulants are co-administered. Appropriate monitoring should be performed when anticoagulants are co-administered. Adjustment of the oral anticoagulant dose may be necessary to obtain the desired degree of anticoagulation.</p> <p>Very rare blood clotting disorders are observed and the frequency of prolongation of the bleeding time and prothrombin time was not known.</p>
Lack of efficacy due to resistance	<p>The number of cases of acquired resistance (the ability of microorganism to resist the activity of a particular antimicrobial agent to which it was previously susceptible) in individual species may vary geographically and over time. Thus, local information on the resistance situation is required, particularly for the adequate treatment of severe infections. If, based on the local resistance situation, the efficacy of penicillin G is questionable, expert therapeutic advice should be sought. Particularly in cases of serious infection or unsuccessful therapy, a microbiological diagnosis should be sought, with the detection of the pathogen and its susceptibility to penicillin G.</p>

Table 13-7 Missing information

Risk	What is known
Effect on fertility	No studies have been performed to investigate the effect of penicillin G sodium on fertility.

13.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

13.2.6 Part VI.2.6 Planned post authorization development plan

None

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

N/A