VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Bacterial pharyngitis

Pharyngitis is inflammation of the pharynx, causing a sore throat.Pharyngitis is primarily caused by bacteria and viruses. When evaluating a patient with a sore throat, it is important to differentiate pharyngitis caused by Group A streptococcus {is a bacterium often found in the throat and on the skin (GAS)} from that caused by other pathogens (a bacterium, virus, or other microorganism that can cause disease). GAS is the most common cause of pharyngitis that is treatable with antibiotics. During the winter, approximately 15-25% of all cases of pharyngitis in children will be due to streptococcal (type of bacteria) infection. In adults this number is closer to 10%. Pharyngitis is most common in individuals aged 5-15 years, although adults may also acquire the disease. Streptococcal pharyngitis (an infection of the back of the throat including the tonsils) is very uncommon in children younger than 3 years.

Acute bacterial sinusitis

Sinusitisis characterized by inflammation of the lining of the paranasal sinuses (group of four large air filled space above and behind the nose). Because the mucous membrane of nose is simultaneously involved and because sinusitis rarely occurs without concurrent rhinitis (irritation and inflammation of the mucous membrane inside the nose). Acute sinusitis affects 3 in 1000 people in the United Kingdom. Chronic sinusitis affects 1 in 1000 people. Sinusitis is more common in winter than in summer. Rhinoviral infections (mostly associated with the common cold) are prevalent in autumn and spring. Corona viral infection (infection in nose, sinuses, or upper throat) occurs mostly from December to March. Women have more episodes of infective sinusitis than men because they tend to have more close contact with young children. The rate in women is 20.3%, compared with 11.5% in men. Common signs and symptoms of sinusitis include thick nasal mucus, a plugged nose, and pain in the face.

Acute exacerbation of chronic bronchitis (AECB)

Bronchitis is characterized by inflammation of the bronchial tubes (bronchi), the air passages that extend from the trachea into the small airways and alveoli. According to estimates from national interviews taken by the National Center for Health Statistics in 2006, approximately 9.5 million people, or 4% of the population, were diagnosed with chronic bronchitis. These statistics may underestimate the population of chronic obstructive pulmonary disease (Lung disorder in which the flow of air to the lungs is blocked) by as much as 50%, because many patients underreport their symptoms and their conditions remain undiagnosed. Acute bronchitis is common throughout the world, though bronchitis occurs more frequently in populations with a low socioeconomic status and in people who live in urban and highly industrialized areas. Chronic bronchitis is more prevalent in people older than 50 years. Several potential triggers for AECB have been identified, including bacterial, viral and atypical pathogens, environmental conditions and worsening of heart problem.

Mild to moderate community acquired pneumonia

Pneumonia is a common lung infection affecting primarily the tiny air bags within the lungs. Pneumonia acquired infectiously from normal social contact that is called community acquired pneumonia. Community-acquired pneumonia (CAP) is one of the most common infectious diseases and is an important cause of mortality and morbidity worldwide. A study using a nationwide claims database to determine the incidence of CAP in the Netherlands identified 195,372 cases of CAP between 2008 and 2011. This represented an average incidence of 295 cases per 100,000 populations per year. It was concluded that the mean annual cost of CAP in this population was 178 million euros, with a disproportionate amount (76%) of the cost being incurred by people older than 50 years. Advanced age is associated not only with a higher incidence of CAP but also with more severe disease, greater need for hospitalization, and higher mortality.

Skin and soft tissue infections

Skin and soft tissue infections (SSTIs) are common in outpatient clinic and emergency department visits and include a wide variety of infections of the various layers of skin, fascia (structure of connective tissue that surrounds muscles) and muscle. SSTIs usually result from traumatic, surgical or healthcare-related skin break down with secondary infection with microorganisms.

Among hospitalized or critically ill patients, 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). Another two studies, including only "superficial" and "deep and/or healthcare- associated" infections, have shown that about 2.0%-5.8% of hospitalized SSTI patients are admitted to the ICU.

Helicobacter pylori (*H. pylori*) associated ulcers:

H. pylori are spiral-shaped bacteria that cause infection in the stomach and that grow in the digestive tract and have a tendency to attack the stomach lining. *H. pylori* infections are usually harmless, but they're responsible for the majority of ulcers in the stomach and small intestine. In north European and North American populations, about one-third of adults are still infected, whereas in south and east Europe, South America, and Asia, the prevalence (proportion of a population found to have a condition) of *H. pylori* is often higher than 50%. *H. pylori* remain highly prevalent in immigrants coming from countries with high prevalence of *H. pylori*. However, the lower prevalence of infection in the younger generations suggests a further decline of *H. pylori* prevalence in the coming decades. Low socioeconomic conditions in childhood are confirmed to be the most important risk factors for *H. pylori* infection.

VI.2.2 Summary of treatment benefits

The efficacy and safety of clarithromycin, 250 mg twice a day, were compared with those of reference drugs, cefadroxil and erythromycin, in studies. In first study, clarithromycin or

cefadroxil 500 mg twice a day was given for 5-14 days and in second study, clarithromycin or erythromycin, 250 mg four times a day, was given for < or = 14 days. In the first study, efficacy and safety were evaluated in 299 and 538 patients, respectively. In the second study, the numbers were 141 and 261 patients, respectively. Overall, clarithromycin was as effective and safe as cefadroxil and erythromycin.

In a study, total 97 children with community-acquired pneumonia including 26 with *Mycoplasma pneumoniae* infection, 15 with *Chlamydia pneumonia* infection, and 6 with mixed *mycoplasma* and *chlamydia* infections were treated with clarithromycin for 10 days at a dose of 15 mg/kg/day given twice daily and erythromycin for 10 days at a dose of 30-50 mg/kg/day given 4 times daily. Clarithromycin showed efficacy equivalent to erythromycin for the treatment of *mycoplasma* or *chlamydia* pneumonia in children.

VI.2.3 Unknowns relating to treatment benefits

The safety of clarithromycin for use during pregnancy and breast-feeding of infants has not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Agranulocytosis (Severe reduction in number of white blood cells which makes infections more likely)	Agranulocytosis (Severe reduction in number of white blood cells which makes infections more likely) has been reported with use of Clarithromycin with an unknown frequency (cannot	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines as your dose may need to be changed or you may need to have regular

Risk	What is known	Preventability
	be estimated from the available data))	blood tests performed.
Risk of increased toxicity in patient with severe hepatic failure in combination with renal impairment (Increased risk of toxicity in patients with severe liver failure in combination with kidney problems)	In patients taking clarithromycin, liver failure has been reported with an unknown frequency. Abnormal liver function is a common side effect with clarithromycin which may affects up to 1 in 10 people. Yellowing of the skin (jaundice), skin irritation, pale stools, dark urine, tender abdomen or loss of appetite. These may be signs that your liver may not be working properly. A change in the levels of products made by the liver, inflammation of the liver or an inability of the liver to function properly (you may notice yellowing of the skin, dark urine, pale stools or itchiness of the skin) are un common side effects which	Talk to your doctor or, pharmacist before taking Clarithromycin tablets if you have any liver problems or kidney problems Do not take Clarithromycin tablets if you suffer from severe liver disease and kidney disease at the same time Tell your doctor before you start to take this medicine if you have liver problems. If you have liver problems, your doctor may need to reduce your dose. Clarithromycin tablets should not be taken for more than 14 days if you have these problems.

Risk	What is known	Preventability
	may affect up to 1 in 100 people.	
Pseudomembranous colitis (inflammation (swelling, redness) of the large intestine that occurs in some people who have taken antibiotics)	Inflammation of the large intestine has been reported in patients taking antibiotics. In patients taking clarithromycin, inflammation of the colon has been reported with an unknown frequency. Severe or prolonged diarrhoea, which may have blood or mucus in it. Diarrhoea may occur over two months after treatment with clarithromycin.	If you suffer from any of mentioned symptoms at any time during your treatment, stop taking your tablets and contact your doctor immediately. Tell your doctor before you start to take this medicine, If you develop severe diarrhoea while you are taking clarithromycin tablets, or even several weeks after you have stopped taking it.
QT prolongation/ (irregular or change in heart rhythms) Torsades de pointes(change from the normal heartbeat in a distinctive form).	Irregular or change in heart rhythms is an uncommon side effect which may affect up to 1 in 100 people.. When clarithromycin administered together with medicines called terfenadine or astemizole (widely taken for hay fever or allergies) or	Do not take Clarithromycin tablets If you are taking other medicines which are known to cause serious disturbances in heart rhythm. If you have abnormally low levels of potassium or

Risk	What is known	Preventability
	cisapride (for stomach disorders) or pimozide (for mental health problems) can sometimes cause serious disturbances in heart rhythm.	magnesium in your blood (hypokalaemia or hypomagnesaemia) if you or someone in your family has a history of heart rhythm disorders (ventricular cardiac arrhythmia, including torsade de pointes) or abnormality of electrocardiogram (ECG, electrical recording of the heart) called "long QT syndrome" If you have an irregular heart rhythm. Before taking clarithromycin, inform to your doctor, if you have heart problems, in particular heart rhythm problems (e.g. long QT syndrome).
Interaction with ergot alkaloids: risk of ergot toxicity (Drugs used for treatment of migraine	Co-administration of clarithromycin with ergotamine or	Do not take Clarithromycin tablets if you are taking ergotamine-like drugs

Risk	What is known	Preventability
[severe headache])	dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm (Narrowing of blood vessels due to spasm of vessel walls), and ischaemia (Low oxygen in tissue due to decreased blood circulation caused by obstruction) of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated.	(usually used for migraine)
Interaction with statins metabolized by CYP3A4: risk of rhabdomyolysis [Interaction with statins (a class of drugs often prescribed by doctors to help lower cholesterol levels in the blood) metabolized by CYP3A4 (an important enzyme in the body, mainly found in the liver and in	Clarithromycin should not be used together with atorvastatin, rosuvastatin (HMG-CoA reductase inhibitors, commonly known as statins, and used to lower levels of cholesterol (a type of fat) in the blood). Statins can cause rhabdomyolosis (a condition	Do not take Clarithromycin tablets if you are taking simvastatin or lovastatin (to reduce cholesterol). If your treatment with clarithromycin cannot be avoided then therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Risk	What is known	Preventability
the intestine): risk of rhabdomyolysis (breakdown of muscle fibers)].	which causes the breakdown of muscle tissue which can result in kidney damage) and signs of myopathy (muscle pain or muscle weakness) should be monitored.	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines as your dose may need to be changed or you may need to have regular tests performed.
Interaction with midazolam and other triazolobenzodiazepines metabolized by CYP3A4: risk of excessive sedation [interaction with midazolam and other triazolobenzodiazepines (a class of drugs primarily used for treating anxiety) metabolized by CYP3A4 (an important enzyme in the body, mainly found in the liver and in the intestine): risk of excessive sedation (calmness)]	Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines as your dose may need to be changed or you may need to have regular tests performed. Monitoring the patient for increased CNS pharmacological effects is suggested.

Risk	What is known	Preventability
	for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely. There have been post-marketing reports of drug interactions and central nervous system (CNS) effects {(e.g., somnolence (Sleepiness) and confusion)} with the concomitant use of clarithromycin and triazolam.	
Interaction with colchicine: risk of colchicine toxicity {Interaction with colchicine (a medicine used for treating gout (a disease of joints)}	There have been post-marketing reports of colchicine toxicity (undesirable effects) with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with kidney problems. Deaths have been reported in some patients. Clarithromycin may lead to	Before starting the treatment with clarithromycin, inform to your doctor, if you took or recently taken colchicines. Patients should be monitored for clinical symptoms of colchicine toxicity. Do not take Clarithromycin tablets if you are taking colchicine (to treat gout).

Risk	What is known	Preventability
	increased exposure to colchicine.	
Interaction with oral anticoagulant: risk of hemorrhage. [Interaction with oral anticoagulant (Drug used to stop blood from clotting): risk of hemorrhage (heavy bleeding)]	There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio(a calculation based on results of a prothrombin time) and is used to monitor individuals who are being treated with the blood-thinning medication) and prothrombin time which help to diagnose the cause of unexplained bleeding or inappropriate blood clots)when clarithromycin is co-administered with warfarin	INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants at a same time. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines as your dose may need to be changed or you may need to have regular tests performed: - Warfarin
Severe immediate hypersensitivity reactions (severe allergic reactions)	This is an uncommon side effect which may affect more than 1 in 1000 to less than 1 in 100 patients. A rash, difficulty breathing, fainting (feeling weak and	Do not take clarithromycin tablets if you are allergic to clarithromycin, other macrolide (class of drug same as clarithromycin) antibiotics (e.g. erythromycin or

Risk	What is known	Preventability
	dizzy) or swelling of the face and throat. This is a sign that you may have developed an allergic reaction.	azithromycin, or any of the other ingredients of this medicine. During the treatment with clarithromycin, inform to your doctor immediately if you experienced any allergic reaction.
Antimicrobial resistance (Resistance to those agents that kills microorganisms or inhibits their growth)	Long-term use may, as with other antibiotics, result in colonization (by which a species spreads to new areas) with increased numbers of non-susceptible bacteria and fungi. Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide (class of antibiotics) drugs, as well as lincomycin (used to treat severe bacterial infections) and clindamycin (used to treat severe bacterial infections).	In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides (class of drug same as clarithromycin), it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia (lung infection). In hospital acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Risk	What is known	Preventability
	For the eradication of *H. pylori* the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.	
Acute pancreatitis [(Inflammation of pancreas (the organ that makes hormones, including insulin, and digestive juices)]	Inflammation of the pancreas has been reported with use of Clarithromycin with an unknown frequency (frequency cannot be estimated from the available data).	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines as your dose may need to be changed or you may need to have regular tests performed.
Serious skin hypersensitivity reactions (SJS and TEN) [Serious skin allergic reactions (skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth) and (loss of skin that	These side effects are reported with use of Clarithromycin with unknown frequency. Severe skin reactions such as blistering of the skin, mouth, lips, eyes and genitals (symptoms of a rare allergic	If you suffer from severe skin reactions such as blistering of the skin, mouth, lips, eyes and genitals (symptoms of a rare allergic reaction called Stevens-Johnson syndrome/toxic epidermal necrolysis)at any time

Risk	What is known	Preventability
leaves patches that look like a burn)	reaction called Stevens-Johnson syndrome/toxic epidermal necrolysis)	during your treatment, then stop taking your tablets and contact your doctor immediately:
Acute renal failure (Kidney failure)	Kidney failure is reported with use of clarithromycin with unknown frequency Other less common side effects included inflammation of the kidney or an inability of the kidney to function properly (you may notice tiredness, swelling or puffiness in the face, abdomen, thighs or ankles or problems with urination).	Do not take Clarithromycin tablets if you have severe kidney disease at the same time. If you have severe kidney problems your doctor may need to reduce your dose. Clarithromycin tablets should not be taken for more than 14 days if you have these problems. Tell your doctor before you start to take this medicine if you have kidney problems.
Drug related severe hepatic disorders(Drug related severe liver problems)	Yellowing of the skin (jaundice), skin irritation, pale stools, dark urine, tender abdomen or loss of appetite. These may be signs that your	Do not take Clarithromycin tablets if you have severe liver disease.

Risk	What is known	Preventability
	liver may not be working properly. Abnormal liver function is a common side effect which may affect up to 1 in 10 people A change in the levels of products made by the liver, inflammation of the liver, an inability of the liver to function properly or liver failure (you may notice yellowing of the skin, dark urine, pale stools or itchiness of the skin) are un common side effects which may affects up to 1 in 100 people.	

Important potential risks

Risk	What is known
Cardiovascular events (Problems related to heart and blood vessels)	Cardiac arrest (Stopping of the heart to pumping blood around your body.), atrial fibrillation (abnormal heart rhythm), electrocardiogram QT

Risk	**What is known**
	prolonged (Abnormal ECG heart tracing),extrasystoles (an extra heartbeat), palpitations (irregular heartbeats) are uncommon side effects which may affects more than 1 in 1000 to less than 1 in 100 patients. Torsade de pointes (Life-threatening irregular heart beat), ventricular tachycardia (rapid heartbeat that arises from improper electrical activity of the heart) and ventricular fibrillation (heart rhythm problem that occurs when the heart beats with rapid electrical impulses) are reported with use of clarithromycin with unknown frequency
Psychiatric disorders	Insomnia (lack of sleep) is a common side effect which may affects more than 1 in 100 to less than 1 in 10 patients. Anxiety, nervousness, screaming are uncommon side effects which may affects more than 1 in 1000 to less than 1 in 100 patients Psychotic disorder (disease causing abnormal thinking and perceptions), confusional state, depersonalization (dream-like feeling), depression, disorientation, hallucination (seeing things that are not really there),, abnormal dreams and mania are reported with use of clarithromycin with unknown frequency (cannot be estimated from the available

Risk	What is known
	data)
Interaction with oral hypoglycemic agents/insulin: risk of hypoglycemia {interaction with oral glucose lowering agents: risk of abnormal decrease in sugar in the blood, which can cause weakness, fatigue, and if severe, can cause loss of consciousness)}	Oral hypoglycemic agents/Insulin with certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme (an important enzyme in the body, mainly found in the liver and in the intestine) by clarithromycin may be involved and could cause hypoglycemia when used at a same time.

Missing information:

Risk	What is known
Use during pregnancy and lactation	The safety of clarithromycin for use during pregnancy has not been established. As per non-clinical studies, the possibility of adverse effects on embryofoetal (unborn baby from 2 to 8 weeks) development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk. The safety of clarithromycin for using during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

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

No studies planned.

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

Version	Date	Safety Concerns	Comment
3.0	12-December-2016	No change in safety concern.	RMP has been updated as per revised SPC and PIL Day 120 comments.
2.0	13 September 2016	Following safety concerns were removed ***Important identified risks*** • Hypokalaemia (risk of prolongation of QT-time). • Deterioration of myasthenia gravis	Risk Management Plan has been updated as per RMS Day 70 and day 100 comments. .

Version	Date	Safety Concerns	Comment
		Following safety concerns were added ***Important identified risks*** • Agranulocytosis • Acute pancreatitis • Serious skin hypersensitivity reactions (SJS and TEN) • Acute renal failure • Drug related severe hepatic disorders • Interaction with midazolam and other triazolobenzodiazepines metabolized by CYP3A4: risk of excessive sedation • Interaction with oral anticoagulant: risk of hemorrhage ***Important Potential risks*** • Cardiovascular events • Psychiatric disorders • Interaction with oral	

Version	Date	Safety Concerns	Comment
		hypoglycemic agents/insulin: risk of hypoglycemia **Following safety concerns were modified** • Important identified risk "Severe hepatic failure in combination with renal impairment" has been updated as "Risk of increased toxicity in patient with severe hepatic failure in combination with renal impairment" • Important identified risk "History of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes has been updated as "QT prolongation/ Torsades de pointes" • Important identified risk "Drug Interactions: Concomitant use of: Astemizole, cisapride, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias including	

Version	Date	Safety Concerns	Comment
		ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Concomitant use of: Clarithromycin and ergotamine or dihydro-ergotamine as this may result in ergot toxicity. Concomitant use of HMG-CoA reductase inhibitors (statins): Lovastatin or simvastatin, due to the risk of rhabdomyolysis. Treatment with these agents should be discontinued during clarithromycin treatment. Concomitant use of colchicine in combination with renal- or hepatic impairment has been updated as "Interaction with ergot alkaloids: risk of ergot toxicity "Interaction with statins metabolized by CYP3A4: risk of rhabdomyolysis" "Interaction with colchicine: risk of colchicine toxicity"	

Version	Date	Safety Concerns	Comment
		• Important identified risk "Known hypersensitivity to macrolide antibiotic drugs or to any of its excipients" has been updated as "Severe immediate hypersensitivity reactions" • Important identified risk "Resistance to antibiotics has been updated as "Antimicrobial resistance" • Important identified risk "Exposure in pregnancy (1st trimester) has been updated as an missing information "Use during pregnancy and lactation"	