VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risks:	
	QTc prolongation
	Use in patients with hepatic impairment and risk of fatal hepatic failure
	Use in patients with renal impairment and acute renal failure
	Pseudomembranous colitis
	Emerging resistance, including cross resistance between clarithromycin and other macrolide drugs as well as lincomycin and clindamycin.
	Anaphylaxis
	Severe cutaneous reactions
	Psychiatric disorders
	Drug interactions
	Ototoxicity
Important potential risks:	
	Use in immunocompromised patients
Missing information:	
	Use in Pregnancy and lactation

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
QTc prolongation	(Proposed) content in SPC: Included in section **4.3 Contraindications** **4.4 Warning** Listed in **section Interaction with other medicinal products and other forms of interaction 4.5** Listed **in section 4.8 Undesirable effects** **Listed in section 4.9 Overdose** **Prescription only medicine.**	None proposed
Use in patients with hepatic impairment and risk of fatal hepatic failure	(Proposed) content in SPC: Included in section **4.3 Contraindications** **4.4 Warning** Listed **in section 4.8 Undesirable effects** Included in sections **5.2 Pharmacocinetic poperties and 5.3 Preclinical safety data** **Prescription only medicine.**	None proposed
Use in patients with renal impairment and acute renal failure	(Proposed) content in SPC: Included in section **4.2 Posology and method of administration** **4.4 Warning** Listed **in section 4.8 Undesirable effects and** included **in 5.2 Pharmacocinetic poperties** **Prescription only medicine.**	None proposed
Pseudomembranous colitis	(Proposed) content in SPC: Included in section **4.4 Warning** Listed **in section 4.8 Undesirable effects** **Prescription only medicine.**	None proposed
Emerging resistance, including cross resistance between clarithromycin and other macrolide drugs as well as lincomycin and clindamycin.	(Proposed) content in SPC: Included in section **4.4 Warning** Listed in section **4.8 Undesirable effects** **Prescription only medicine.**	None proposed
Anaphylaxis	(Proposed) content in SPC: Included in section **4.3 Contraindications** **4.4 Warning** Listed **in section 4.8 Undesirable effects** **Prescription only medicine.**	None proposed
Severe cutaneous reactions	Proposed) content in SPC: Included in section	None proposed

	4.3 Contraindications **4.4 Warning** Listed **in section 4.8** **Undesirable effects** **Prescription only medicine**	
Psychiatric disorders	(Proposed) content in SPC: Listed **in section 4.8** **Undesirable effects** **Prescription only medicine.**	None proposed
Drug interactions	(Proposed) content in SPC: Included in section **4.3 Contraindications** **4.4 Warning** Listed **in section Interaction with other medicinal products and other forms of interaction 4.5** **Listed in section 4.8** **Undesirable effects** **Prescription only medicine.**	None proposed
Ototoxicity	Included in section **4.4 Warning** Listed in section **Interaction with other medicinal products and other forms of interaction 4.5** Listed in section **4.8** **Undesirable effects** **Prescription only medicine.**	None proposed
Important potential risk		
Use in immunocompromised patients	(Proposed) content in SPC: **Listed in section 4.8** **Undesirable effects** **Prescription only medicine.**	None proposed
Missing information		
Use in pregnancy and lactation	(Proposed) content in SPC: Included in section **4.4 Warning** **4.6 Fertility, pragnancy and lactation** **Prescription only medicine.**	None proposed

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Upper respiratory tract infection (URTI) is a nonspecific term used to describe acute infections involving the ear, nose, sinuses (air-filled passageways in the bones around the nose and eyes), and pharynx. The illnesses are known as the common cold, the throat infection (tonsillitis, pharyngitis) middle ear infection (otitis), and sinusitis.
URTI is the most frequent disease presented in general practice and is mainly caused by viruses and an incidence rate ranging from 69 to 133 per 1000 over the years. The incidence

rate was consistently highest in young children, varying from 237 to 550 per 1000 over the years. Women presented URTI slightly more frequently than men consistently over time. The case-control study revealed that in 53% of URTI cases a virus could be isolated and in 18% a pathogenic bacteria.

Bacterial pharingitis

Bacteria Group A beta-hemolytic streptococci cause 5% to 10% of cases of pharyngitis in adults and 20-30% in children. Approximately 0.5% to 2% of viral sinusitis results in subsequent sinusitis caused by bacteria.

Sinus infection (Acute bacterial sinusitis) is short-lived infection of the sinuses, air-filled passageways in the bones around the nose and eyes. Viruses cause most such infections. Viral illness can be complicated with bacterial infection. Approximately 0.5 % to 2% of viral sinusitis results in subsequent sinusitis caused by bacteria.

Acute exacerbations of chronic bronchitis

This infection is bacterial worsening of chronic (long lasting) bronchitis. It is inflammation of the airways that carry air to lungs. It causes a cough that often brings up mucus, as well as shortness of breath, wheezing, and chest tightness. Respiratory viruses are the most common causes of acute bronchitis, and cigarette smoking is indisputably the predominant cause of chronic bronchitis. Chronic bronchitis is seen in 3.4% to 22.0% of adults. This wide range of prevalence estimates may be due to varying definition.

Community-acquired pneumonia (an infection of the lungs that is caught outside of hospital) is a common disease, with an annual incidence of 5 to 11 cases per thousand adults.

Pneumonia is a common illness in all parts of the world. Every year about 5 million people die of acute respiratory infections. Among these, pneumonia represents the most frequent cause of death among all age groups. People most at risk are older than 65 or younger than 2 years of age, or already have health problems. In the United Kingdom, the annual incidence of pneumonia is approximately 6 cases for every 1000 people for the 18–39 age groups. For those over 75 years of age, this rises to 75 cases for every 1000 people.

Uncomplicated (mild to moderate severity) skin and soft tissue infections

Skin infections are folliculitis (folliculitis is inflammation of one or more hair follicles. It can occur anywhere on the skin), cellulitis (inflammation of the deeper layers of the skin), erysipelas (inflammation of the upper layers of the skin). The bacteria enter the body when one get an injury such as a bruise, burn, surgical cut, animal bites or wound. The epidemiology is less completely defined and may differ from those in industrialized countries and in developing countries. Community-acquired (is caught outside of hospital) skin and soft tissue infections are most commonly caused by bacteria staphylococci or streptococci, but almost any organism is capable of causing inflammation within soft tissue. Recent epidemiological trends have shown an increase not only in meticillin-resistant Staphylococcus aureus (MRSA), but also in MRSA acquired in the community. Factors that may affect the microbial cause include underlying disease such as diabetes or immune dysfunction; hospital attendance, injecting drug use, travel, animal contact and environmental contamination.

Peptic ulcer disease (PUD) refers to a disruption of the mucosal integrity of the stomach, duodenum, or both, caused by local inflammation, which leads to a well-defined mucosal defect. Major causes of PUD are infection by *Helicobacter pylori* bacteria and nonsteroidal anti-inflammatory drugs (NSAIDs).

Peptic ulcer disease is extremely common and in developed countries the annual incidence is one to three per 1.000 of the population. It affects about one in ten men and one in 15 women in Europe at some stage in their lives. Some 250,000 hospital admissions

annually are due to the disease. Complications of ulcers still claim the life of some 25,000 people each year in the EU. In Europe, prevalence rates for *H. pylori* infection range from approximately 30 to 60 per cent.

VI.2.2 Summary of treatment benefits

The clarithromycin is used to treat certain infections caused by bacteria, including infections of the throat, infections of sinuses, bronchi, skin and lungs and for the eradication of *Helicobacter pylori* in peptic ulcer. Clarithromycin is in a class of medications called macrolides antibiotics. It works by stopping the growth of bacteria. Antibiotics do not work for colds, flu, or other viral infections. Clarithromycin is available as 250 mg and 500 mg film-coated tablets. The medicine can only be obtained with a prescription.
Prescribers should consider official guidance on the use of antibacterial agents and local levels of resistance (resistance of a bacteria to an antibiotic that was originally effective for treatment of infections caused by it) to antibiotics. Clarithromycin was as effective as the comparator antibiotics in many studies.
Recommended antibiotic therapy in pharyngitis and sinusitis are beta-lactams and macrolides represent an alternative to beta-lactams in patients allergic to penicillin.
In community-acquired pneumonia macrolide is offered as an alternative choice (in atypical pneumonia) and for those patients who are hypersensitive to penicillin.
Prompt initiation of antibiotics in patients with bacterial pharyngitis decreases contagion and may prevent development of complications, such as peritonsillar (a swollen area within body tissue, containing an accumulation of pus) abscess. Therapy with antibiotic is also important to preventing immunological complications, such as rheumatic fever (a noncontagious acute fever marked by inflammation and pain in the joints) and glomerulonephritis (inflammation of kidneys).

VI.2.3 Unknowns relating to treatment benefits

The substance clarithromycin has been used for many years. The safety of clarithromycin is essentially comparable to that of standard therapies for patients receiving the currently registered dosage and for whom contraindications and precautions of use (as in the product label) are taken into account.
No differences were observed between males and females, no special precaution is necessary in the elderly. The use of clarithromycin tablets has not been studied in children under the age of 12 years (clarithromycin tablets are not appropriate pharmaceutical form for these population). The safety of clarithromycin during pregnancy and breast-feeding has not been established. There is no data available on the effect of clarithromycin on fertility in humans.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
A heart rhythm disorder that can potentially cause fast, chaotic heartbeats **(QTc prolongation,)**	Clarithromycin can cause prolongation of the QT interval and potentially related clinical conditions (increased heart rate and deadly torsades the pointes). There are the following situations may lead to increased risk of heart rhythm disorders and clarithromycin should	Yes, talked with patients about all medicines that might they take before prescribing clarithromycin and by monitoring for early symptoms of certain heart conditions (e.g. severe heart problems or "QT prolongation").

	not be given to patients or should be used with caution: - Concomitant administration of clarithromycin and any of the following active substances should not be given: astemizole, cisapride, pimozide and terfenadine. - Clarithromycin should not be given to patients with history of irregular heart beat (QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes). - Clarithromycin should not be given to patients with electrolyte disturbance, particularly in cases of low blood potassium levels and low blood magnesium levels. - In patients taking other medicines known to affect the way of heart beats (quinidine, disopyramide) - Clarithromycin should be used with caution in patients with cardiac disease (such as coronary artery disease, severe cardiac insufficiency, bradycardia (a very slow heart rate <50 bpm), or when co- administered with other medicinal products known to affect the way of heart beats (quinidine, disopyramide)). - Clarithromycin must not be used in patients born with long QT interval.	Or by monitoring a slow or irregular heartbeat, altered electrolyte levels in the blood, especially low potassium and magnesium levels.
Use in patient with damage or injury of the liver and risk of sever injury of the liver that could cause death. **(Use in patients with hepatic impairment and risk of fatal hepatic failure)**	Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function. Patients with severe hepatic failure in combination with renal impairment should not be treated with clarithromycin. Cases of fatal hepatic failure (patients died) have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.	Yes, by monitoring for early symptoms. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as loss of appetite, yellowing of the skin (jaundice), dark urine, itching, or tenderness in the abdomen.
Use in patient with kidneys impairment and risk of kidneys impairment **(Use in patients with renal impairment and acute renal failure)**	Caution is advised in patients with severe renal impairment. It is known that levels of clarithromycin in blood are higher and excretion of clarithromycin in urine is lower in patients with kidneys impairment. Clarithromycin should not be used in patients who suffer from severe	Yes, by dose adjustment by monitoring for early symptoms. Clarithromycin must be discontinued immediately and appropriate medical therapy instituted.

	hepatic failure in combination with kidneys impairment. There have been rare reports of kidney problems such as raised levels of protein normally excreted by the kidneys or raised levels of kidney enzymes and reports of inflammation of the kidney (which can cause swollen ankles or high blood pressure) or kidney failure.	
Inflammation of the large intestines associated with the use of antibiotics **(Pseudomembranous colitis)**	Clostridium difficile-associated diarrhea, sometimes called Pseudomembranous colitis, has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. It is an inflammation of the intestines that occurs following antibiotic treatment and is caused by toxins produced by the bacterium *Clostridium difficile*. Symptoms of antibiotic-associated colitis usually begin four to ten days after antibiotic treatment has begun. Diarrhoea may occur over two months after treatment with clarithromycin.	Yes, by monitoring for early symptoms. If severe or prolonged diarrhoea develop, which may have blood or mucus in it, during or after taking clarithromycin film-coated tablets, clarithromycin must be discontinued immediately, as these could be symptoms of more serious conditions such as pseudomembranous colitis or clostridium difficile associated diarrhoea. Patient needs appropriate medical therapy.
Emerging resistance, including cross resistance between clarithromycin and other macrolide drugs as well as lincomycin and clindamycin	Sometimes an infection caused by bacteria does not respond to a course of an antibiotic because the bacteria causing the infection are resistant to the antibiotic that is being taken. This means that they can survive and even multiply despite the antibiotic. Bacteria resistant to one antibiotic can become resistant to other antibiotic (this we call **cross resistance**). If some bacteria survive they can cause the infection to come back. In view of the emerging resistance of *Streptococcus pneumoniae* bacteria to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. Skin and soft tissue infections of mild to moderate severity are most often caused by bacteria *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Long-term use may, result in increased numbers of non-susceptible	Yes, by using antibiotics carefully. This can help to reduce the chance of bacteria becoming resistant to them. It is important to take every dose to fight the infection. If it becomes clear that bacteria are resistant to clarithromycin, it is necessary to begin the appropriate treatment.

	bacteria and fungi. Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.	
Life-threatening type of allergic reaction **(Anaphylaxis)**	Clarithromycin can cause all kind of allergic reactions. Cases of acute hypersensitivity reactions, such as anaphylaxis (swelling of the lips, face, throat, tongue, rash, swallowing or breathing and wheezing problems.	Yes, by monitoring for early symptoms of allergic reaction. In case developing a rash, itching, hives, difficulty breathing, fainting or swelling of the face and throat, clarithromycin must be discontinued immediately and consult the doctor as these may be signs of an sever allergic reaction and may need emergency treatment.
Severe cutaneous reactions (such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms – DRESS)	Severe bullous skin reactions such as Stevens-Johnson syndrome (which looks like a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals including mucosal reactions) or toxic epidermal necrolysis (the more severe form, causing extensive peeling of the skin) and drug rash with eosinophilia (increased specific type of white blood cell in blood) and systemic symptoms – DRESS have been reported.	Yes, by monitoring for early symptoms of allergic reaction. a rash, itching, hives, inflammation or peeling of the skin, ulceration of the mouth, lips and skin, fever clarithromycin must be discontinued immediately and consult the doctor as these may be signs of an sever cutaneous reaction and may need emergency treatment.
Psychiatric disorders	There have been reports of psychotic disorder and depersonalization related to clarithromycin and frequency with not known (adverse reactions from post-marketing experience; cannot be estimated from the available data).	Yes, by monitoring for early symptoms of psychotic disorder such as confusion, change in sense of reality, depression, loss of bearings (disorientation), hallucinations (seeing things), abnormal dreams (nightmares), manic episodes. Clarithromycin must be discontinued immediately and consult the doctor.
Drug interactions	Concomitant administration of clarithromycin and any of the following active substances should not be taking: astemizole, cisapride, pimozide and terfenadine as this may result in a heart rhythm disorders. Clarithromycin should not be used concomitantly with ergotamine or dihydroergotamine because this can cause toxicity due to ergot (vasospasm, and ischemia of the extremities and other tissues	Yes, not to treat the patient with clarithromycin if he/she is taking one of the following drugs: astemizole, cisapride, pimozide and terfenadine, HMG-CoA reductase inhibitors (statins), ergotamine or dihydtoergotamine, colchicine, ticagrelor, renolazine, triazolobenzodiazepines such as triazolam and midazolam, other ototoxic drugs (especially amynoglycosides).

	including the central nervous system) either burning pains or eventually gangrene in the limbs or itching skin and seizures. Clarithromycin concomitant with lovastatin or simvastatin should not be used. Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis (breakdown of muscle tissue) has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of statin. Colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency, some with a fatal outcome. Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam. There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Caution is advised regarding concomitant administration of clarithromycin with other (ear-poisoning) drugs, especially with aminoglycosides. Monitoring of spinning sensation and ringing in the ears or hearing loss should be carried out during and after treatment. The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant decrease in blood sugar (hypoglycemia). There is a risk of serious hemorrhage when clarithromycin is co-	If patient is treated by some other drugs such as warfarin (used in thin blood), drugs and insulin in diabetic patiens and some other drugs (metabolised in liver), especially care is needed and it may be necessary to do blood tests. Clarithromycin must be discontinued immediately and consult the doctor if developed unexpected or unusual symptoms.

	administered with warfarin. Drugs that are inducers of CYP3A4 (e.g. rifampicin, phenytoin, carabamazepin, phenobarbital, St. Johns wort) may increase the metabolism of clarithromycin. This may result in decreased levels of clarithromycin in blood leading to a reduced efficacy. Furthermore it might be necessary to monitor the plasma levels of these drugs, which could be increased due to clarithromycin.	
Deafness and impaired imbalance (Ototoxicity)	Both hearing and balance can be disrupted, especially when clarithromycin is given with other ototoxic drugs (e.g. aminoglycosides)	Yes, by monitoring for early symptoms of impaired hearing or tinnitus, or imbalance and consult the doctor if one of these symptoms developed.

Important potential risks:

Risk	**What is known (Including reason why it is considered a potential risk)**
Use in immunocompromised patients (patients with decressed immunity)	In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial (e. g. tuberculosis) infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

Missing information

Risk	**What is known**
Use in Pregnancy and lactation	The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk. The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted into human breast milk. There is no data available on the effect of clarithromycin on fertility in humans. In rats, the limited data available do not indicate any effects on fertility.

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

Not applicable. No postauthorisation studies are planned.

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

Not applicable, this is the first Risk management plan.