Elements for a public summary

VI.2.1 Overview of disease epidemiology

Upper respiratory tract infection 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), pharynx, and bronchi. The illnesses are known as the common cold, otitis, tonsillitis, pharyngitis, and sinusitis. Acute otitis media (short-lived infection of the ear) is very common in childhood. It is the most common condition warranting medical therapy in children less than five years of age. Three out of four children will have at least one ear infection by their third birthday. Adults can also get ear infections, but they are less common. Adults develop an average of two to four colds annually. Viruses cause most Upper respiratory tract infection. Viral illness can be complicated with bacterial infection. If bacteria are the cause, antibiotics should help.
Group A beta-hemolytic streptococci (bacteria) 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 [(1)].

Lowe respiratory tract infection: bacterial worsening of chronic bronchitis and bacterial pneumonia. The first one 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. Chronic bronchitis is seen in 3.4% to 22.0% of adults. This wide range of prevalence estimates may be due to varying definitions [(2)].
Pneumonia is an infection in one or both of the lungs. People most at risk are older than 65 or younger than 2 years of age, or already have health problems. 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 in Europe and Northern America [(3)].

Skin and soft tissue infections, as folliculitis (folliculitis is inflammation of one or more hair follicles. It can occur anywhere on the skin), inflammation of the deeper layers of the skin (cellulitis), 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, or wound. The epidemiology is less completely defined and may differ from those in industrialized countries and in developing countries.

Sexually transmitted disease caused by an organism called Chlamydia is inflammation of the urethra and cervix. Symptoms in men are: burning sensation during urination, discharge from the penis or rectum, testicular tenderness or pain, rectal discharge or pain. Symptoms in women are: burning sensation during urination, painful sexual intercourse, rectal pain or discharge, vaginal discharge. Both males and females may have chlamydia without having any symptoms (70% of women, 25% of men). As a result, infection passes from partner to partner without knowing it. Chlamydia infection can cause serious, permanent damage to a woman's reproductive organs.
Chlamydia infection is the most common sexually transmitted disease in the United States. Sexually active individuals and individuals with multiple partners are at highest risk. It is estimated that 1 in 15 sexually active females aged 14-19 years has chlamydia [(4)].

VI.2.2 Summary of treatment benefits

This product contains the active substance azithromycin. It is available as 250 mg film-coated tablets. The medicine can only be obtained with a prescription.

Azithromycin is an antibiotic belonging to the class of macrolides. Azithromycin works by inhibiting the growth of the bacteria. The full list of bacteria against which Azibiot is active can be found in the summary of product characteristics. Prescribers should consider official guidance on the use of antibacterial agents and local levels of resistance to antibiotics. Antibiotics will not kill viruses that can cause colds, flu, or other infections.
Prompt initiation of antibiotics in patients with strep pharyngitis decreases contagion and may prevent development of complications, such as peritonsillar abscess. Therapy with antibiotic is also important to preventing immunological complications, such as rheumatic fever and glomerulonephritis. Azithromycin was as effective as the comparator antibiotics (e.g. amoxicillin, amoxicillin/clavulanic acid, clarithromycin) in many studies for upper respiratory tract infections (98-100%)[5], lower respiratory tract infections [6], skin and soft tissue infections and Chlamydia infection [7]. Chlamydia infection can cause infertility or serious problems with pregnancy. Babies born to infected mothers can get eye infections and pneumonia from chlamydia so it is very important to treat this infection. 12 randomized clinical trials of azithromycin versus doxycycline for the treatment of genital chlamydial infection demonstrated that the treatments were equally efficacious, with microbial cure rates of 97% and 98%, respectively [7].

VI.2.3 Unknowns relating to treatment benefits

The substance azithromycin has been used for many years. Many studies have been performed and a lot of data have been obtained from the patients treated with this drug. The patient with special conditions, such as liver disease, long QT syndrome and aarrhythmia (disruption of the heartbeat), anaphylaxis (allergic), and Clostridium difficile associated diarrhea (an inflammation of the gut) are considered to be well evaluated. There is a lack of studies in pregnant and brest-feeding women. Also there is not enough safety data in children less than 45 kg with azithromycin 250 mg tablets therefore this pharmaceutical form is not recommended to them.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Arrhythmia, torsades de pointes, QT prolonged (life-threatening irregular heart beat (torsades de pointes), abnormal ECG heart tracing (QT prolongation)	Cardiac arrhythmia (irregular heart beat) and torsades de pointes occurs in very rare cases, it is a known and listed adverse event and is described especially in intravenous administration. Therefore azithromycin should not be used: • in patients with irregular heart beat • with other active substances that prolong QT interval • in patients with electrolyte disturbance, particularly in cases of hypokalaemia (low blood potassium concentration) and hypomagnesaemia	Yes, by monitoring for early symptoms of certain heart conditions (e.g. severe heart problems or "QT prolongation"). Or by monitoring a slow or irregular heartbeat, altered electrolyte levels in the blood, especially low potassium and magnesium levels.

	(low blood magnesium concentration) • in patients with clinically relevant bradycardia (heart rate of under 60 beats per minute) • severe cardiac insufficiency (heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body)	
Hepatic Impairment (hepatic disorders (hepatic failure, hepatic necrosis), inflammation of the liver (hepatitis)	Signs and symptoms of liver dysfunction are rapid developing weakness associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy (a condition, usually occurring secondarily to advance liver disease, marked by disturbances of consciousness that may progress to deep coma). Patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. The use of azithromycin should be undertaken with caution in patient with significant hepatic disease.	Yes, by monitoring liver function tests/investigations and for early symptoms of abnormal hepatic function, yellowing of the skin or eyes. Azithromycin administration should be stopped if liver dysfunction has emerged.
Clostridium difficile associated diarrhea (pseudomembranous colitis)	Antibiotic-associated colitis is a consequence of an inflammation of the intestines that sometimes occurs following antibiotic treatment and is caused by toxins produced by the bacterium *Clostridium difficile*. Azithromycin may cause diarrhea (antibiotics may change the normal intestinal flora so they can cause diarrhoea), and in some cases it can be severe and persistent. It may occur 2 months or more after the use of antibiotic. In these cases it is probably due to *Clostridium difficile.*	Yes, by monitoring diarrhea. If it is watery or bloody, severe and persistent, azithromycin should be stopped and patient should call the doctor. Patient should not use any medicine to stop diarrhea unless doctor has told him.
Serious allergic reactions (Anaphylaxia)	Anaphylaxis is a severe, whole-body life-threatening allergic reaction. Anaphylaxis happens	Yes, by monitoring for early symptoms of allergic reaction. If such symptoms

	quickly after the exposure. Tissues in different parts of the body release histamine and other substances. This causes the airways to tighten and leads to other symptoms: abdominal pain, abnormal (high-pitched) breathing sounds, anxiety, chest discomfort or tightness , cough, diarrhea, difficulty breathing, difficulty swallowing, dizziness or light-headedness, hives, itchiness, nasal congestion, nausea or vomiting, palpitations, skin redness, slurred speech, swelling of the face, eyes, or tongue, unconsciousness, wheezing. Anaphylaxis is an emergency condition that needs professional medical attention right away. Azithromycin can cause all kind of allergic reactions.	occur (swelling face, mouth and throat) azithromycin should be stopped and contact doctor or emergency department immediately.
Serious cutaneous adverse reactions	Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (rarely resulting in death) have been reported in association with azithromycin therapy.	Azithromycin therapy needs to be discontinued and doctor contacted immediately, if the patients gets severe skin rash causing redness blistering and flaking.
Drug rash with eosinophilia and systemic symptoms syndrome (**DRESS syndrome)**	DRESS syndrome is a severe idiosyncratic drug reaction with a long latency period. Usually appear 2 to 8 weeks after introduction of the triggering drug. It is followed by a variety of clinical signs: fever, rash, hematological findings (eosinophilia, leukocytosis, etc.), and abnormal liver function tests. The cutaneous manifestations typically consist of an urticarial, maculopapular eruption and, in some instances, vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma . Visceral involvement (hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis) is the major cause of	The doctor should be aware of the possibility of this syndrome if the patient gets severe skin rash, eosinophilia and disorders in at least 1 internal organ. Azithromycin therapy needs to be discontinued.

	morbidity and mortality in this syndrome.	
Azithromycin interaction with digoxin (used to treat heart failure) and **cyclosporine** (used to suppress the immune system to prevent and treat rejection of a transplanted organ or bone marrow)	Concomitant administration of azithromycin with digoxin or cyclosporine may increase concentration of digoxin or cyclosporine in blood.	Doctor should be informed of all concomitant medication before onset of azithromycin therapy. If concomitant administration is necessary digoxin and cyclosporine levels in blood can be monitored and doses adjusted, if necessary.
Hearing impairment	Hearing impairment including deafness and/or tinnitus has been reported as possible adverse drug reactions of azithromycin.	If hearing impairment appears doctor needs to be contacted.

Important potential risks:

Risk	**What is known**
Superinfection (a new infection occurring in a patient having a pre-existing infection)	As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended (such as pneumonia, bacterial infection of the throat, inflammation of the gastrointestinal tract, respiratory disorder, inflammation of the mucous membrane inside the nose, a fungal infection of the mouth and vagina).
Azithromycin interaction with medicines belonging to the group of ergot derivatives (e.g. to treat migraine) and medicines **used to prevent blood clots/blood thinning medicines** (Coumarin-type oral anticoagulants such as warfarin)	In patients receiving ergot derivatives, ergotism (effect of long term ergot poisoning) has been precipitated by coadministration of some macrolide antibiotics. Azithromycin and ergot derivatives should not be coadministered. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. More frequent blood coagulation tests may be necessary when azithromycin is used in patients receiving coumarin-type oral anticoagulants such as warfarin.
Pyloric stenosis in newborns (narrowing of the pylorus)	Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (narrowing of the pylorus, the lower part of the stomach through which food and other stomach contents pass to enter the small intestine.) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.
Interaction with CYP3A4 inhibitor Cisaprid	A drug interaction is a situation in which one substance affects the activity of a drug when both are administered together. The combination of azithromycin and Cisaprid (used to increase bowel movement) can increase the potential risk of irregular heart beat

	(torsades de pointes) or abnormal ECG heart tracing (QT prolongation). It is especially important to tell your doctor or pharmacist if you are taking these medicines.
Interaction with Terfenadine	It is especially important to tell your doctor or pharmacist if you are taking *terfenadine* (a medicine for the treatment of allergies). The combination of azithromycin and terfenadine may increase the potential risk of abnormal ECG heart tracing (QT prolongation). Such interactions have been seen in treatment with terfenadine and other macrolides.

Missing information

Risk	**What is known**
Safety and efficacy for the prevention or treatment of Mycobacterium avium Complex in children	Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex (MAC) in children are not known.
Pregnancy and breast-feeding	If you are pregnant or breast-feeding, think you may be pregnant or are planning to have baby, ask your doctor or pharmacist for advice before taking this medicine. There are no controlled studies on use of Azibiot during pregnancy in humans. Since safety during pregnancy has not been established, the doctor will prescribe Azibiot tablets to you only upon careful weighing of the benefit of treatment against a possible risk. Breast-feeding Azithromycin is secreted into human breast milk. Sufficient and adequately controlled clinical studies were not performed in breast-feeding mothers, therefore during the treatment breast-feeding is not recommended.

VI.2.5 Summary of additional 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.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable. No postauthorisation studies are planned.

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

Table: Major changes to the Risk Management Plan over time

Version	***Date***	***Safety concerns***	Comment
1.1	At time of authorisation HU national 22.1.2014	**Important identified risks:** Arrhythmia, torsades de pointes, QT prolonged	

		Hepatic Impairment Clostridium difficile associated diarrhea Anaphylaxia **Important potential risks:** Interaction with CYP3A4 inhibitor Cisaprid Interaction with Terfenadine **Important missing information:** Children under 45 kg Pregnancy and breast-feeding	
1.2	At time of authorisation in SK/H/0148/001-002/DC procedure 6.12.2013	**Important identified risks:** Arrhythmia, torsades de pointes, QT prolonged Hepatic Impairment Clostridium difficile associated diarrhea Anaphylaxia **Important potential risks:** Interaction with CYP3A4 inhibitor Cisaprid Interaction with Terfenadine **Important missing information:** Children under 45 kg Pregnancy and breast-feeding	The same RMP (as in HU national procedure) has been confirmed from SK agency after MAH transfer to Krka d.d. in SK/H/0148/001-002/DC procedure
2.0	New version in line extension procedure in HU national procedure **not confirmed yet**	**After first LoD in HUnational procedure** **Important identified risks:** Arrhythmia, torsades de pointes, QT prolonged including drug-drug interaction with active substances known to prolong QT interval Hepatic Impairment Clostridium difficile associated diarrhea Anaphylaxia Serious cutaneous adverse reactions (SCARs) Drug-drug interaction with digoxin or cyclosporine Hearing impairment Exacerbation and new onset of Myastenia gravis **Important potential risks:**	

		Drug-drug interactions with ergot derivatives, theophylline and coumarin type oral drugs used to prevent the blood clotting **Missing information:** Infants and newborns under 1 year of age Pregnancy and breast-feeding	

1. Sherif B. Mossad. Upper Respiratory Tract Infections. Advances in Pulmonary Medicine. September 25-27, 2013
2. American Journal of Respiratory and Critical Care Medicine; V.187; 2/1/13; p228
3. European Journal of Clinical Microbiology and Infectious Diseases; V.32; 3/13; p305
4. CDC. CDC Grand Rounds: Chlamydia prevention: challenges and strategies for reducing disease burden and sequelae. MMWR Morbidity and mortality weekly report 2011;60:370-3
5. David H Peterset al. Azithromycin: A Review. Drugs 44(5):750-799;1992.
6. Cochrane Database Systemic Review. July 8;2011 Azithromycin for acute lower respiratory tract infection.
7. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. Sex Transm Dis 2002;29:497–502.