PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

AZOTORION (AZITHROMYCIN) 250 MG FILM-COATED TABLETS

ORION OYJ

DATE: 10-09-2015, VERSION 1.1

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Microbial pathogens, such as bacteria, have accompanied humanity for centuries and continue to represent significant causes of morbidity and mortality worldwide. Bacterial infections have significant personal and public health effects. Immunocompromised persons such as diabetic patients, persons with severe illnesses and patients receiving immunosuppressants are more prone to get severe bacterial infections and infection related complications.

Group A streptococci are the leading bacterial cause of pharyngitis in children and adults. Antimicrobial treatment must be administered to eradicate the pathogen from the throat, limit the spread of the infection and prevent possible progression to rheumatic fever, suppurative disease or toxin-mediated complications.

VI.2.2 Summary of treatment benefits

Active ingredient of Azotorion is azithromycin. Azithromycin belongs to the class of medications called macrolide antibiotics. It works by stopping the growth of bacteria. It is used to treat:

- upper and lower airway infections (such as bronchitis, pneumonia, tonsillitis, pharyngitis, sinusitis and middle ear infections)
- skin and soft tissue infections
- sexually transmitted diseases caused by organisms called *Chlamydia trachomatis*

Pathogenic microbial infections may lead to complications, suffering and in serious cases even death. Therefore appropriate and effective treatment is important.

The efficacy of azithromycin has been well documented over many years of widespread clinical use.

VI.2.3 Unknowns relating to treatment benefits

Bacteria strains that are resistant to azithromycin may occur. The prevalence of acquired resistance may vary geographically and with time for selected species. Therefore local information on bacteria's azithromycin resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of azithromycin in at least some types of infections is questionable.

Safety and efficacy of azithromycin for the prevention or treatment of Mycobacterium Avium Complex (a type of lung infection that often affects people with human immunodeficiency virus [HIV]) in children have not been established.

VI.2.4 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Anaphylaxis
	Severe Cutaneous Adverse Reactions (SCARs)
	Hepatic toxicity
	Clostridium difficile associated diarrhoea (CDAD)
	Hearing impairment
	Exacerbation of symptoms of *Myasthenia gravis*
	QT prolongation/Torsade de pointes
	Drug-drug interactions with digoxin and cyclosporine
Important potential risk	Superinfection
	Drug-drug interactions with ergot derivatives and Coumarin-type oral anticoagulants
Missing information	Administration during pregnancy and breast-feeding
	Effect on fertility
	Administration in patients with severe hepatic disease

Important identified risks

Risk	What is known	Preventability
Serious allergic reactions (anaphylaxis)	Like other antibiotics, azithromycin may cause hypersensitivity (allergic) reactions. In rare cases allergic reactions, such as anaphylaxis, may be serious and even life-threatening. Symptoms of anaphylaxis include e.g. itchy rash, throat swelling, and low blood pressure.	Patients who are allergic to azithromycin or any other macrolide antibiotic such as erythromycin or clarithromycin or any of the other ingredients of this medicinal product must not take this medicine. If the patient suspects hypersensitive (allergic) reactions, patient should stop taking azithromycin and contact a doctor. Symptoms of serious allergic reaction requiring immediate medical care are e.g. sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body), and low blood pressure.

Risk	What is known	Preventability
Severe skin reactions (Severe 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 and flaking.
Liver toxicity	Cases of severe liver inflammation potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Signs and symptoms of liver dysfunction can be e.g. rapid developing weakness associated with yellowness of the skin and eye whites, dark urine, bleeding tendency temporary worsening of brain function.	The use of azithromycin should be undertaken with caution in patients with liver disease. If liver problems are suspected doctor may check liver enzyme values and azithromycin therapy will be stopped if necessary.
Severe diarrhoea/bowel inflammation (*Clostridium difficile* associated diarrhoea)	*Clostridium difficile* (certain kind of bacteria) associated diarrhoea has been reported with the use of nearly all antibacterial agents, including azithromycin. Diarrhoea may range in severity from mild diarrhoea to life-threatening bowel inflammation. Severe or prolonged diarrhoea, which may have blood or mucus in it, during or after treatment with azithromycin, may be a sign of serious bowel inflammation.	If diarrhoea or loose stools develop during or after treatment, doctor should be contacted at once.
Hearing impairment	Hearing impairment including deafness and/or tinnitus have been reported as possible adverse drug reactions of azithromycin.	If hearing impairment appears doctor needs to be contacted.
Worsening of symptoms of *Myasthenia gravis* (neurologic condition that may cause muscle	Worsening of the symptoms of *myasthenia gravis* and new onset of myasthenia syndrome have	Before starting azithromycin therapy doctor should be informed if the patient has

Risk	What is known	Preventability
weakness)	been reported in patients receiving azithromycin therapy.	myasthenia gravis.
Abnormal heart rhythm and serious heart rhythm disturbances (QT prolongation / Torsade de pointes)	Abnormal heart rhythm (prolonged QT interval) predisposing to serious heart rhythm disturbances has been seen in treatment with other antibiotics belonging to the same group (macrolides), including azithromycin. Caution is required when treating patients who: • were born with or have had condition with abnormal heart rhythm (seen on ECG, electrical recording of the heart) • are taking other medicines that may cause abnormal ECG changes • have salt imbalance in the blood (especially low level of potassium or magnesium in the blood) • have a very slow heart rhythm (called 'bradycardia'), have a weak heart (heart failure) • are women of elderly patients	Before treatment is initiated patient should inform and discuss with doctor of: • any heart problems currently or in the past • diagnosed prolonged QT interval personally or in family history • all concomitant medications • diagnosed salt imbalance in blood or conditions that may cause disturbances in salt balance
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.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
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.
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.

Missing information

Risk	What is known
Administration during pregnancy and breast-feeding	There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.
Effect on fertility	In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.
Administration in patients with severe liver disease	There are no studies of azithromycin therapy in this patient group.

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.

The Summary of Product Characteristics and the Package leaflet for Azotorion can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment