Part VI: Summary of the risk management plan by product

VI.1 Elements for summary tables in the Public Assessment Report (PAR)

VI.1.1 Summary table of Safety concerns

Table 7: Summary of safety concerns for PAR

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Lower atovaquone plasma levels associated with diarrhoea or difficulty taking with food • Interaction with other medicinal products and other forms of interaction
Important potential risks	• None
Missing information	• Use in pregnancy and lactation • Use in children • Use in elderly • Use in patients with renal or hepatic impairment

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

No post-authorisation efficacy studies are on-going/planned since the active substance has well established use.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of Risk Minimisation Measures

Table 8: Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risk		
Hypersensitivity	Risk minimisation activities described in the relevant section of the SmPC: **Listed in SmPC section 4.3 Contraindications:** Atovaquone 750 mg/5 mL oral suspension is contra-indicated in individuals with known hypersensitivity to atovaquone or to any of the excipients listed in SmPC section 6.1. **Listed in SmPC section 4.8 Undesirable effects:** *Immune System Disorders*	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Common: hypersensitivity reactions including angioedema, bronchospasm and throat tightness. **Other routine risk minimisation measures:** Prescription only medicine.	
Lower atovaquone plasma levels associated with diarrhoea or difficulty taking with food	Risk minimisation activities described in the relevant section of the SmPC: **Listed in SmPC section 4.4 Special warnings and precautions for use:** Diarrhoea at the start of treatment has been shown to be associated with significantly lower atovaquone plasma levels. These in turn correlated with a higher incidence of therapy failures and a lower survival rate. Therefore, alternative therapies should be considered for such patients and for patients who have difficulty taking [Invented name] with food. **Listed in SmPC section 4.8 Undesirable effects:** *Gastrointestinal disorders* Very common: nausea Common: diarrhoea, vomiting **Other routine risk minimisation measures:** Prescription only medicine.	None Proposed
Interaction with other medicinal products and other forms of interaction	Risk minimisation activities described in the relevant section of the SmPC: **Listed in SmPC section 4.4 Special warnings and precautions for use:** Patients receiving concurrent tetracycline should be closely monitored. The concomitant administration of atovaquone and efavirenz or boosted protease-inhibitors should be avoided whenever possible. The concomitant administration of atovaquone and rifampicin or rifabutin is not recommended. Concurrent use of metoclopramide is not recommended. Atovaquone can increase the levels of etoposide and its metabolite. **Listed in SmPC section 4.5 Interaction with other medicinal products and other forms of interaction:** As experience is limited, care should be taken when combining other drugs with Atovaquone.	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Concomitant administration of rifampicin or rifabutin is not recommended as it is known to reduce plasma concentrations of atovaquone levels by approximately 50% and 34%, respectively. Concomitant treatment with metoclopramide has been associated with a significant decrease (about 50%) in plasma concentrations of atovaquone. When given with efavirenz or boosted protease-inhibitors, atovaquone concentrations have been observed to decrease as much as 75%. This combination should be avoided whenever possible. Concomitant treatment with tetracycline has been associated with decreases in plasma concentrations of atovaquone. In clinical trials of Atovaquone small decreases in plasma concentrations of atovaquone (mean < 3 µg/mL) were associated with concomitant administration of paracetamol, benzodiazepines, acyclovir, opiates, cephalosporins, anti-diarrhoeals and laxatives. The causal relationship between the change in plasma concentrations of atovaquone and the administration of the drugs mentioned above is unknown. **Other routine risk minimisation measures:** Prescription only medicine.	
Important Potential Risks		
None		
Missing information		
Use in pregnancy and lactation	Risk minimisation activities described in the relevant section of the SmPC: **Listed in SmPC section 4.6 Fertility, Pregnancy and lactation:** Pregnancy There is no information on the effects of atovaquone administration during human pregnancy. Atovaquone should not be used during pregnancy unless the benefit of treatment to the mother outweighs any possible risk to the developing foetus. Insufficient data are available from animal experiments to assess the possible risk to reproductive potential or performance. Breastfeeding It is not known whether atovaquone is excreted in human milk, and therefore breast feeding is not recommended.	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other routine risk minimisation measures: Prescription only medicine.	

Use in children and adolescents	Risk minimisation activities described in the relevant section of the SmPC: **Listed in SmPC section 4.2 Posology and method of administration:** *Dosage in Children* Clinical efficacy has not been studied. **Other routine risk minimisation measures:** Prescription only medicine.	None Proposed
Use in Elderly	Risk minimisation activities described in the relevant section of the SmPC: **Listed in SmPC section 4.2 Posology and method of administration:** *Dosage in Older people* There have been no studies of atovaquone in the elderly (see section 4.4). **Listed in SmPC section 4.4 Special warnings and precautions for use** No clinical experience of atovaquone treatment has been gained in elderly patients. Therefore use in the elderly should be closely monitored. **Other routine risk minimisation measures:** Prescription only medicine.	None Proposed
Use in patients with renal or hepatic impairment	Risk minimisation activities described in the relevant section of the SmPC: **Listed in SmPC section 4.2 Posology and method of administration:** *Renal or hepatic impairment* Atovaquone has not been specifically studied in patients with significant hepatic or renal impairment. **Other routine risk minimisation measures:** Prescription only medicine.	None Proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pneumocystis jiroveci pneumonia (PJP), formerly known as *Pneumocystis carinii* pneumonia (PCP), is the most common opportunistic infection in persons with HIV infection.

Pneumocystis first came to attention as a cause of interstitial pneumonia in severely malnourished and premature infants during World War II in Central and Eastern Europe. Before the 1980s, fewer than 100 cases of PJP were reported annually in the United States, occurring in patients who were immunosuppressed (eg, cancer patients receiving chemotherapy and solid-organ transplant recipients receiving immunosuppressants). In 1981, the Centers for Disease Control and Prevention reported PJP in 5 previously healthy homosexual men residing in the Los Angeles area.

P jiroveci is now one of several organisms known to cause life-threatening opportunistic infections in patients with advanced HIV infection worldwide. Well over 100,000 cases of PJP were reported in the first decade of the HIV epidemic in the United States in people with no other cause for immunosuppression.

While officially classified as a fungal pneumonia, PJP does not respond to antifungal treatment. Although a histopathologic demonstration of the organism is required for a definitive diagnosis (see Histologic Findings), treatment should not be delayed. Treatment of PJP may be initiated before the workup is complete in severely ill high-risk patients. Treatment of PJP depends on the degree of illness at diagnosis, determined on the basis of the alveolar-arterial gradient. See the A-a Gradient calculator.

Antibiotics are primarily recommended for treatment of mild, moderate, or severe PJP. Trimethoprim-sulfamethoxazole (TMP-SMX) has been shown to be as effective as intravenous pentamidine and more effective than other alternative treatment regimens. Corticosteroids are used as adjunctive initial therapy only in patients with HIV infection who have severe PJP. Preventive measures (eg, smoking cessation and chemoprophylaxis) can play an important role in disease management.

VI.2.2 Summary of treatment benefits

Acute treatment of mild to moderate Pneumocystis pneumonia (PCP, caused by Pneumocystis jiroveci, formerly classified as P. carinii) (alveolar - arterial oxygen tension difference [(A-a) DO2] < 45 mmHg (6 kPa) and oxygen tension in arterial blood (PaO2) ≥ 60 mmHg (8 kPa) breathing room air) in patients who are intolerant of co-trimoxazole therapy.

VI.2.3 Unknowns relating to treatment benefits

Data are not available for use in children. No specific studies have been performed in pregnant and lactating females. There are no adequate data from elderly patients.

VI.2.4 Summary of safety concerns

Table 9: Important identified risks

Risk in Lay Language (Clinical Term)	What is known	Preventability
Allergic reactions (Hypersensitivity reactions)	There is a risk of allergic reactions associated with the use of this medicinal product.	Yes, patients should not use this medicinal product if they are allergic to the active ingredient or excipients of the medicinal product.
Lower atovaquone levels in the blood associated with loose stools (diarrhoea) or difficulty taking with food	Diarrhoea at the start of treatment may result in higher incidence of therapy failures and a lower survival rate.	Alternative therapies should be considered for such patients and for patients who have difficulty taking this medication with food.
Interaction with other medicinal products and other forms of interaction	Some products that may interact with this drug. Other medications can affect the removal of atovaquone from your body, which may affect how atovaquone works. Examples include efavirenz, rifampin, rifabutin, metoclopramide, tetracycline, among others. This medication can speed up the removal of other medications from your body, which may affect how they work. An example of an affected drug is indinavir. Other medications may also be affected.	Yes, this medicinal product should be used with caution with other medicines.

Important potential risks:
None

Table 10: Missing information

Risk in Lay Language (Clinical Term)	What is known
Use during pregnancy and breast-feeding (Use during pregnancy and lactation)	During pregnancy, this medication should be used only when clearly needed. Discuss the risks and benefits with your doctor. It is not known whether this drug passes into breast milk. Consult your doctor before breast-feeding.
Use in children	Atovaquone 750 mg/5 mL oral suspension is not recommended for use in children as there is no clinical experience.
Use in patients above 65 years (Use in Elderly)	Atovaquone 750 mg/5 mL oral suspension is not recommended for use in patients above 65 years as there is no clinical experience.
Use in patients with damaged kidney or liver functions (Use in patients with renal or hepatic impairment)	Atovaquone 750 mg/5 mL oral suspension is not recommended for use in patients with damaged kidney or liver functions as there is no clinical experience.

VI.2.5 Summary of risk minimisation measures by safety concern

The Summary of Product Characteristics (SmPC) of atovaquone 750 mg/5 mL oral suspension provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them.

This medicinal product has no additional risk minimisation measures for any of mentioned safety concerns.

VI.2.6 Planned post authorisation development plan

No post authorisation studies are planned for this product.

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

Changes to the Risk Management Plan over time is provided in the table below.

Version	Date	Safety Concerns	Comments
V1	09-Jun-2016	**Important Identified Risks** • Hypersensitivity • Diarrhoea • Interaction with other medicinal products and other forms of interaction **Important Potential Risks** • None **Missing Information** • Use in pregnancy and lactation • Use in children • Use in elderly • Use in patients with renal or hepatic impairment	First version of the RMP.
V1.1	15-Nov-2016	Change in the following safety concern: **Important Identified risk** • 'Diarrhoea' changed to 'Lower atovaquone plasma levels associated with diarrhoea or difficulty taking with food'.	Based on the RMS Day 70 Preliminary Assessment report, the safety concern was updated. All relevant sections of the RMP have been updated accordingly. Statement regarding pharmaco-vigilance activities removed from summary tables. Other changes include – Part I updated to include version and sign-off date. Addition of List of abbreviations. Annexure renumbering to be consistent with the "Guidance on format of the risk management plan (RMP) in the EU – in integrated format". Minor formatting corrections done in the RMP.