VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Malaria is caused by mosquito bites whereby the malaria parasites can enter the body and then live in body tissues such as red blood cells or the liver.

Malaria is a common and life-threatening disease in many tropical and subtropical areas. The World Health Organization (WHO) reports that malaria is currently endemic (i.e., constantly occurring) in over 100 countries, which are visited by more than 125 million international travellers annually. According to the WHO, many international travellers fall ill with malaria each year while visiting countries where the disease is endemic, and well over 10,000 travellers fall ill with malaria after returning home. Early diagnosis of malaria and its effective and timely treatment reduces the severity of the disease and prevents associated deaths.

There are various alternatives for both the prevention of malaria, or the treatment of malaria which include chloroquine, quinine, artesunate, artemether, mefloquine, doxycycline and clindamycin. When selecting treatment, official guidelines and local information on the prevalence of resistance to antimalarial drugs should be taken into consideration. Official guidelines will normally include World Health Organisation (WHO)and public health authorities' guidelines.

VI.2.2 Summary of treatment benefits

Atovaquone and proguanil are used to both prevent and treat malaria and work by interfering with two different methods used by the malaria parasites to grow and multiply. These medications are used to kill the malaria parasites living inside red blood cells and other tissues.

The benefits of effective treatments are to reduce the severity of symptoms and complications associated with malaria and to prevent death from malaria. Using these two treatments together for the treatment of malaria is more beneficial than using either treatment alone.

Atovaquone/Proguanil Hydrochloride tablets combine these two products into a single, fixed dose combination treatment and are especially recommended for the prevention and treatment of malaria caused by Plasmodium falciparum where the parasite may be resistant to other antimalarial drugs.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe allergic reactions including facial and throat swelling and symptoms such as falling blood pressure.	Occasionally, severe allergic reactions have been reported in patients taking Atovaquone/ Proguanil Hydrochloride tablets.	These reactions are not predictable and therefore cannot be prevented. In patients who experience allergic reactions, Atovaquone/ Proguanil treatment should be discontinued promptly and appropriate treatments for allergy initiated.
Significant decreases in red and white blood cells and blood platelets associated with use of Atovaquone/Proguanil Hydrochloride tablets in patients with severe reductions of kidney function.	In patients with very poor kidney function, there is a significant slowing of the rate at which proguanil is excreted from the body. As a response to this, the drug may build up in the body with each dose administered (accumulation).	Preventable by avoidance of product in patients with very poor kidney function. Atovaquone/Proguanil should not be used for malaria prevention in patients known to have very poor kidney function. For treatment of malaria, alternative treatments should be used if at all possible.
Severe skin reactions	Mild skin rashes and "hives" (urticaria) have been commonly reported with Atovaquone/ Proguanil Hydrochloride tablets. Severe skin reactions which include severe blistering and/or skin loss and may rarely be life-threatening have been reported. It is not known how commonly this occurs although it is likely to be rare.	These reactions are not predictable and therefore cannot be prevented.
Convulsions	Convulsions (seizures) have been reported but it is uncertain if these are definitely caused by Atovaquone/ Proguanil Hydrochloride tablets	These reactions are not predictable and therefore cannot be prevented.

Risk	What is known	Preventability
Hallucinations	Hallucinations have been reported but it is uncertain if these are definitely caused by Atovaquone/ Proguanil Hydrochloride tablets	These reactions are not predictable and therefore cannot be prevented.
Liver inflammation	Abnormalities of liver function tests (liver enzymes) have been reported commonly with Atovaquone/ Proguanil Hydrochloride tablets. Sometimes this may indicate liver inflammation (hepatitis). Hepatitis has also been reported but it is uncertain if this is definitely caused by Atovaquone/ Proguanil Hydrochloride tablets	These reactions are not predictable and therefore cannot be prevented.
Increased bleeding in patients already on Warfarin (anticoagulant).	Warfarin is a commonly used medication in patients who have had blood clotting problems such as deep vein thrombosis, or pulmonary emboli, or where there is a high risk of clotting (e.g. some forms of heart disease, or following surgery). Occasionally, proguanil interferes with warfarin leading to increased anti-clotting effects and the possibility of bleeding.	Caution should be used when starting or stopping Atovaquone/ Proguanil Hydrochloride tablets in patients also taking warfarin.
Feeling of low mood (depression)	In clinical studies, depression was reported commonly with Atovaquone/ Proguanil Hydrochloride tablets.	These reactions are not predictable and therefore cannot be prevented.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
No potential risks have been identified.	

Important missing information

Risk	What is known
Experience in patients with severe reduction in liver function	Studies indicate that no dosage adjustments are needed in patients with mild to moderate disturbances in liver function. No studies have been conducted in patients with severe reduction in liver function, although no special precautions or dosage adjustments are anticipated to be needed.
Treatment of severe and complicated forms of malaria	Atovaquone/Proguanil Hydrochloride tablets have not been studied for the treatment of malaria affecting the brain (cerebral malaria) or other severe, complicated forms of malaria including malaria with very high parasite levels, malaria associated with lung complications or with kidney failure.
Experience of use during pregnancy	There is no adequate information concerning the safety of Atovaquone/Proguanil Hydrochloride tablets used during pregnancy, either for the mother or for the unborn baby. Studies in animals have not shown any strong evidence of harmful effects, although unexplained toxic effects were seen in pregnant rabbits.
Experience in lactating women	Atovaquone has been shown to pass into the milk in rat studies, however it is not known if this also occurs in humans, or if this would be associated with safety concerns for the breast-fed infant.

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.

The Summary of Product Characteristics and the Package leaflet for Atovaquone/Proguanil Hydrochloride tablets can be found in the Atovaquone/Proguanil Hydrochloride tablets EPAR page.

This medicine has no additional risk minimisation measures.

Atovaquone and proguanil in combination has been used extensively in clinical practice. The safety profile of this combination has been clearly established both in the prevention and treatment of malaria caused by *Plasmodium falciparum.* No new or unexpected safety concerns have been discovered.

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

None are planned

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

Not applicable.