

SCHEDULING STATUS

S2

PROPRIETARY NAME AND DOSAGE FORM

Mozitec Film-coated Tablets

COMPOSITION

Each film-coated tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride.

Inactive ingredients:

Microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, poloxamer 188, povidone, colloidal silicon dioxide, magnesium stearate and opadry brown (hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, ferric oxide).

PHARMACOLOGICAL CLASSIFICATION

A 20.2.6 Medicines against protozoa

PHARMACOLOGICAL ACTION

Pharmacodynamics:

Atovaquone and proguanil hydrochloride, interfere with two different pathways involved in the biosynthesis of pyrimidines required for nucleic acid replication. The mechanism of action of atovaquone against *P. falciparum* is at mitochondria level, via inhibition of mitochondrial electron transport at the level of the cytochrome bc₁ complex, and collapse of mitochondrial membrane potential. One mechanism of action of proguanil, via its metabolite cycloguanil, is inhibition of dihydrofolate reductase, which disrupts deoxythymidylate synthesis. This causes the inhibition of DNA synthesis.

Pharmacokinetics:**Absorption:**

The pharmacokinetics of atovaquone are comparable between healthy subjects and HIV-infected patients. Although there are no atovaquone bioavailability data in healthy subjects, in HIV-infected patients the absolute bioavailability of a 750 mg single dose of atovaquone tablets taken with food is 21 % (90 % CI: 17- 27 %). Dietary fat taken with atovaquone increases the rate and extent of absorption, increasing AUC 2-3 times and C_{max} 5 times over fasting.

Proguanil hydrochloride is well and extensively absorbed regardless of food intake.

Distribution:

Atovaquone is highly protein bound (> 99 %) but does not displace other highly protein bound medicines *in vitro*, indicating significant interactions arising from displacement are unlikely. The volume of distribution of atovaquone is $0,62 \pm 0,19$ L/kg. Proguanil is 75 % protein bound. In human plasma, the binding of atovaquone and proguanil were unaffected by the presence of the other.

Metabolism:

There is no evidence that atovaquone is metabolised, and only trace amounts appear in the in urine with parent substance being predominantly (>90 %) eliminated unchanged in faeces. Proguanil hydrochloride is partially metabolised with less than 40 % being excreted unchanged in the urine. Its metabolites cycloguanil and 4-chlorophenylbiguanide are also excreted in the urine.

Pharmacokinetics in the elderly:

There is no clinically significant change in the average rate or extent of absorption of atovaquone or proguanil between elderly and young patients. Systemic availability of

cycloguanil is higher in the elderly compared to young patients, but there is no change in its elimination half-life (see DOSAGE AND DIRECTIONS FOR USE).

Pharmacokinetics in hepatic impairment:

In patients with mild to moderate hepatic impairment there is no clinically significant change in exposure to atovaquone when compared to healthy patients. In patients with mild to moderate hepatic impairment there is an increase in proguanil AUC with no change in its elimination half-life and there is a decrease in C_{max} and AUC for cycloguanil. No data are available in patients with severe hepatic impairment (see DOSAGE AND DIRECTIONS FOR USE).

Pharmacokinetics in renal impairment:

In patients with mild to moderate renal impairment, oral clearance and/or AUC data for atovaquone, proguanil and cycloguanil are within the range of values observed in patients with normal renal function. Atovaquone C_{max} and AUC are reduced in patients with severe renal impairment. The elimination half-lives for proguanil and cycloguanil are prolonged in patients with severe renal impairment with corresponding increases in AUC, resulting in the potential of accumulation with repeated dosing (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS

Mozitec is indicated for the prophylaxis of drug-sensitive and drug-resistant *Plasmodium falciparum* malaria.

Official guidelines and local information on the prevalence of resistance to antimalarial medicines should be taken into consideration.

CONTRA-INDICATIONS

Mozitec is contra-indicated in known hypersensitivity to atovaquone or proguanil hydrochloride or any of the ingredients. **Mozitec** is contra-indicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance < 30 ml/min).

WARNINGS AND SPECIAL PRECAUTIONS

Safety and efficacy of **Mozitec** for the prophylaxis of malaria in patients who weigh less than 40 kg has not been established. A repeat dose of **Mozitec** should be taken if vomiting occurs within 1 hour of dosing. In the event of recrudescence of infections due to *P. falciparum* or failure of chemoprophylaxis, patients should be treated with a different blood schizonticide. If diarrhoea occurs, normal dosing should be continued. Absorption of atovaquone may be reduced in patients with diarrhoea or vomiting, but diarrhoea or vomiting was not associated with reduced efficacy for malaria prophylaxis.

However, patients with diarrhoea or vomiting should be advised to continue to comply with personal protection measures (repellents, bednets). It is not recommended that mothers receiving **Mozitec** breast-feed their babies.

Patients are advised to continue to use normal preventative measures i.e. mosquito repellents, window and bed nets when visiting areas known / suspected to be malaria infected.

The concomitant administration of **Mozitec** and rifampicin or rifabutin is not recommended (see INTERACTIONS)

Effects on ability to drive or use machines

No studies have been done to investigate the effect of **Mozitec** on driving performance or the ability to operate machinery, a prediction on detrimental effect on such activities cannot be made on the pharmacology of the ingredients of **Mozitec**.

INTERACTIONS

Concomitant use of tetracycline, metoclopramide, rifampicin and rifabutin may result in decrease in plasma-atovaquone concentrations (see WARNINGS AND SPECIAL PRECAUTIONS). Concomitant administration of atovaquone and indinavir results in a decrease in the C_{min} of indinavir (23 % decrease; 90 % CI: 8 - 35 %). Caution should be exercised in prescribing atovaquone with indinavir due to the decrease in trough levels of indinavir. Atovaquone is highly protein bound (> 99 %) but does not displace other highly protein bound medicines *in vitro*, indicating that significant interactions arising from displacement are unlikely.

PREGNANCY AND LACTATION

The safety of Mozitec when administered concurrently in human pregnancy and lactation have not been established.

DOSAGE AND DIRECTIONS FOR USE

The daily dose should be taken with food or milk at the same time each day. Should vomiting occur within 1 hour of dosing, a repeat dose should be taken.

Prophylaxis:

Prophylaxis should start 1 to 2 days before entering a malaria-endemic area, and be continued daily until 7 days after leaving the area.

Dosage in adults:

One **Mozitec** tablet daily.

Dosage in the elderly:

No dosage adjustments are needed in the elderly (see pharmacokinetics).

Dosage in hepatic impairment:

No dosage adjustments are needed in patients with mild to moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment.

Dosage in renal impairment:

No dosage adjustments are needed in patients with mild to moderate renal impairment.

For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (see CONTRA-INDICATIONS).

SIDE EFFECTS

Mozitec contains atovaquone and proguanil hydrochloride, therefore, the adverse events associated with each of these compounds may be expected with **Mozitec**. At the doses employed for prophylaxis of malaria, adverse events are generally mild and of limited duration. There is no evidence of added toxicity following concurrent administration of atovaquone and proguanil.

Blood & lymphatic system disorders:

Less frequent: Anaemia, neutropenia pancytopenia.

Immune system disorders

Less frequent: angioedema

Endocrine disorders

Less frequent: hyponatraemia

Gastrointestinal disorders

Frequent: Abdominal pain, nausea, vomiting, diarrhoea, gastric intolerance, oral ulceration, stomatitis

Hepatobiliary disorders:

Less frequent: Elevated liver enzymes, elevated amylase levels

Metabolism and nutrition disorders:

Frequency unknown: Anorexia

Nervous system disorders:

Frequent: Headache, insomnia

General disorders and administrative site conditions:

Frequent: Fever

The following adverse events have been reported, the frequency is unknown:

Respiratory, thoracic and mediastinal disorders:

Cough

Skin and subcutaneous tissue disorders:

Rash (including urticaria), hair loss

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In case of suspected overdose, treatment is symptomatic and supportive, given as appropriate.

IDENTIFICATION

Mozitec Tablets: Pinkish brown to brown coloured, circular, biconvex bevelled edge film-coated tablets with '404' debossed on one side and 'G' debossed on the other side.

PRESENTATION

Mozitec Tablets are packed in white HDPE containers with white caps containing 100 tablets. **Mozitec** Tablets are packed in PVC/PVDC (Clear) film backed with push through Aluminium foil blister containing 12 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep out of reach of children.

REGISTRATION NUMBER

47/20.2.6/1014

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue, Centurion

0157

DATE OF PUBLICATION OF THE PACKAGE INSERT

2 June 2020