



Maloff Protect 250mg/100mg film-coated tablets (atovaquone/ proguanil hydrochloride)

Public Consultation

Proposal to make available from Pharmacies

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency responsible for regulating medicines and medical devices. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public reclassification reports. Suspected side-effects to any drug or vaccine can be reported to MHRA by both healthcare professionals and members of the public via the Yellow Card Scheme (<http://www.mhra.gov.uk/yellowcard>)

Ref: ARM93

Maloff Protect 250mg/100mg film-coated Tablets (atovaquone/ proguanil hydrochloride) Proposal to make available from Pharmacies without prescription

We want to know what you think

- Maloff Protect will be used in the prevention of malaria in adults travelling to areas where malaria is prevalent.
- Maloff, which contains the same active ingredients as Maloff Protect is only at the moment available on prescription.
- We propose to make Maloff Protect available in pharmacies.
- The MHRA considers that this product can be available as a Pharmacy medicine.
- We want to know what you think about this change.

Please tell us your views – please use the form at the end of this document.

The deadline for comments is **6 April 2017**.

In this document there is:

- A summary of the proposed change and the background
- A copy of the patient information leaflet and label proposed if the change goes ahead
- A form for your response

The full name of the medicine is Maloff Protect 250mg/100mg film-coated tablets– in this document, we will call it 'Maloff Protect.'

Contents:

1. Background about deciding where medicines are available
2. About Maloff Protect
3. Proposal to make Maloff Protect available as a Pharmacy medicine
4. How was the proposal assessed for Maloff Protect being available as a Pharmacy medicine?
5. Further details on the application
6. What do you think?

Product details:

Product name: Maloff Protect 250mg/100mg film-coated tablets

Active substances: Atovaquone/ proguanil hydrochloride

Licence holder: Glenmark Pharmaceuticals Europe Limited

Route of sale/supply: Current – on prescription (POM); Proposed – Pharmacy (P)

Indication: To prevent malaria in adults weighing more than 40 kg travelling to areas where malaria is widespread.

Marketing Authorisation Number: PL 25258/0166 - 0014

Consultation is open from: 16 March 2017 – 6 April 2017

Reference: ARM93

Contact: reclassification@mhra.gsi.gov.uk

1. Background on deciding where medicines are available

The role of MHRA

MHRA regulates medicines and medical devices in the UK, on behalf of the UK Licensing Authority. This means that MHRA decides whether medicines are available:

- on prescription only - 'prescription only medicine' (POM)
- bought from pharmacies - 'pharmacy medicine' (P)
- bought from other shops - 'general sales list medicine' (GSL)

What is re-classification of a medicine?

Making a change on where a medicine is available is called 'reclassification'. This is sometimes referred to as 'switching'. To decide on this change, MHRA may:

- take advice from its committees of external experts
- take advice from a group ('stakeholder group') of health professionals and representatives of people affected by the classification change
- run a public consultation

To be reclassified from POM to P, a medicine must:

- be unlikely to be a direct or indirect danger to human health when used without the supervision of a doctor, even if used correctly
- be generally used correctly (ie not frequently or to a wide extent used correctly)
- not contain substances or preparations of substances where the activity of the product or its side effects require further investigation
- not normally be prescribed by a doctor for injection (parenteral administration)

What evidence is needed?

A company or organisation can ask MHRA for a medicine to be available as a pharmacy medicine or a general sale medicine. To do this, they need to get together evidence to show that the medicine

- a) is likely to be used appropriately, and
- b) with relatively little danger to the public.

This evidence needs to focus on the risk to the public. This includes evidence on the possible abuse or misuse of the medicine. The evidence may include:

- clinical studies
- evidence showing acceptable level of side effects
- advice of experts
- views of relevant health professionals and their professional bodies
- views of relevant public associations and individuals with an interest in the medicine under consideration.

Who makes the final decision?

The final decision on whether to approve a change is made by the MHRA, on behalf of the UK Licensing Authority.

2. About Maloff Protect

Maloff Protect is a medicine used to prevent malaria infection in adults travelling to areas where malaria is widespread. This medicine is currently a Prescription Only Medicine.

Malaria is a serious disease caused by parasite passed to humans by the bite of an infected mosquito which passes the malaria parasite into the bloodstream. Maloff Protect prevents malaria by killing these parasites in the blood.

The Commission on Human Medicines has advised the MHRA that this product can be available as a Pharmacy medicine. This report outlines the background to this decision. Please tell us your

views by using the response form at the end of this document (Annex 1). The deadline for comments is **6 April 2017**.

The patient information leaflet and label are provided in Annex 2 and 3.

What is in Maloff Protect?

Maloff Protect is a tablet containing two active ingredients, atovaquone and proguanil hydrochloride.

This is the first application for a product containing atovaquone and proguanil hydrochloride to be available in the UK without prescription.

What are atovaquone and proguanil hydrochloride used for?

Atovaquone and proguanil hydrochloride belong to a group of medicines called antimalarials. They act in different ways to kill the malaria parasite. When used together to prevent malaria they are more effective than when each substance is used alone. They are also used to treat a malaria infection but Maloff Protect will only be available as a P medicine for malaria prevention. It is considered that anyone infected with malaria should be treated under the supervision of a doctor or other healthcare professional qualified to prescribe medicines.

3. Proposal to make Maloff Protect available as a Pharmacy medicine

Who has made the proposal?

The licence-holder for Maloff Protect (Glenmark Pharmaceuticals Europe Limited) has applied to make this product available through Pharmacies.

What are the details of this change?

The application proposes to make Maloff Protect available through Pharmacy outlets for:

- For oral use
- For prevention of malaria in adults weighing more than 40 kg
- Dose: 1 tablet to be taken daily commencing one to two days prior to entering malaria-endemic area, continuing during the period of stay, continuing for 7 days after leaving the area'
- Maximum dose: 250mg/100mg
- Maximum daily dose: 250mg/100mg
- Maximum pack size: 36 tablets (total number of tablets dispensed dependent on duration of travel with maximum of 93 tablets for 12 weeks travel).

4. How was the proposal assessed for Maloff Protect being available on as a Pharmacy medicine?

To be reclassified from POM to P, a medicine must:

- be unlikely to be a direct or indirect danger to human health when used without the supervision of a doctor, even if used correctly
- be generally used correctly (ie not frequently or to a wide extent used correctly)
- not contain substances or preparations of substances where the activity of the product or its side effects require further investigation
- not normally be prescribed by a doctor for injection (parenteral administration)

These criteria are set out in the Human Medicines Regulations 2012, regulation 62(3).

Assessment of suitability for Pharmacy availability

The MHRA assessed the application against these criteria for reclassification:

Direct danger

“Direct danger” means that a danger may be present if the product causes adverse reactions that are important. The most frequently reported side effects for Maloff Protect are generally mild to moderate in intensity and stop when the medicine is stopped; these include abdominal pain, headache, loss of appetite, nausea, vomiting, diarrhoea, and coughing.

Individuals who are considered to be at risk of serious adverse reactions with atovaquone and proguanil hydrochloride will not receive Maloff Protect unless advised by a doctor or other qualified prescriber. These individuals include people weighing less than 40kg, people known to have kidney or liver disease and people with a history of depression or seizures. Maloff Protect will also not be made available to women who are pregnant, planning to become pregnant or breastfeeding. They will be advised to consult their doctor. Children will also not receive this product through pharmacies because they are at risk of more severe complications of malaria and need advice from a doctor or other qualified prescriber.

Although drug-drug interactions (interactions between atovaquone or proguanil hydrochloride and other drugs taken at the same time) have been identified, people who are known to be using any of the drugs known to interact with atovaquone or proguanil would also not receive Maloff Protect. Therefore the danger of drug-drug interactions leading to adverse reactions is low for this product.

Indirect danger

Indirect danger to human health, even when the product is used correctly, could occur where treatment might mask or hide an underlying condition requiring medical attention and supervision. Use of the medicine might delay diagnosis and definitive treatment and jeopardise the chance of more successful therapy. Therefore it is important that the condition or symptoms, for which a medicinal product not subject to a medical prescription is indicated, can be correctly assessed by the patient and that the product can be used without medical supervision.

Maloff protect will be used to prevent and not treat malaria, so no diagnosis of a condition is needed. However, it is important that travellers can decide if Maloff Protect is a correct product to take depending on the part of the world they will be visiting. The label and the patient leaflet advises patients to get advice from a healthcare professional about which antimalarial to take. And training material will be made available for pharmacists and their staff to enable them to identify the correct choice of products for an individual. There is always a risk that people can still catch malaria even if they take medicines to protect themselves. Maloff Protect does not mask the symptoms of malarial infection.

Malaria is a medical emergency, with a potential for life threatening or fatal disease if not treated within 24 hours. Patients will be made aware of the symptoms of malaria at the time of supplying Maloff Protect in case they catch the disease. They will be instructed to seek medical assistance immediately if they experience any of these symptoms and to tell the doctor of the possible exposure to malarial infection. The leaflet will also instruct patients to seek medical advice immediately if they experience any of the symptoms of malaria infection.

As with antibiotics there is a risk that overuse and misuse can lead to resistance (the ability of the malaria parasite to resist the effects of Maloff Protect). The risk that use of Maloff Protect to prevent malaria will lead to the development of resistance is very low. Resistance development is associated with use of antimalarials in treatment rather than prevention of malaria. Patients will be instructed on how to take the medicine correctly, which will also reduce the risk of development of resistance.

Maloff Protect is considered to be safe in long term use provided there are no serious side effects experienced.

Incorrect use – frequently and to a very wide extent

Although patients may be supplied a large number of tablets at once especially for longer trips, the risks of misuse including use for self-treatment are low and no different from that of the prescription medicine. As Maloff Protect has a simple dosing schedule the risk of medication error (mistakes made when using the medicine) is low. The effects of overdose are known to be non-

serious and reversible. Atovaquone and proguanil hydrochloride are not known to have abuse potential.

There is no evidence that similar products already available via pharmacies for prevention of malaria are used incorrectly.

Activity and/or adverse reactions require further investigation

Products containing atovaquone and proguanil hydrochloride have been used as prescription products since 1997 and the activity and adverse reactions are well established therefore this criterion does not apply.

Is normally prescribed as an injection

This product is for oral use only, so this does not apply.

5. Further details on the application

Risk Management Plan

The application contains a risk management plan (RMP). RMPs are documents that contain information on a medicine's safety profile and one or more of the following:

- how any risks identified in the safety profile will be prevented or minimised in patients
- plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine
- risk factors for side effects
- measuring the effectiveness of measures taken to prevent or minimise risks.

The RMP for this product has identified the main risks associated with the product and proposes how these will be managed in the product information (SmPC, labelling and patient information leaflet) and by the provision of training material for pharmacists and their staff.

Label and leaflet

The patient information leaflet and label are provided in Annex 2 and 3.

Summary of Product Characteristics

The Summary of Product Characteristics is provided in Annex 4. This document is a description of Maloff Protect's properties and the conditions attached to its use. It is used as a reference by healthcare professionals.

Training resources

Additional resources will also be provided for pharmacists which cover the following areas:

- Pharmacy Guide
 - The Pharmacy Guide will provide information to pharmacists on the choice of medicines available to prevent malaria and how to use Maloff Protect safely.
 - The Pharmacy Guide includes information on malaria and how it is spread, advice to avoid getting bitten by mosquitoes, the choice of products available to prevent malaria, recommended online resources to seek information from, advice on patients who should not receive Maloff Protect, symptoms of malaria, what to do if patients think they are infected and the importance of reminding patients to take the drug correctly to reduce the risk of resistance.
- Screening Questionnaire
 - The Screening Questionnaire contains a list of Yes/No questions which the pharmacist should ask the patient.
 - This will help the pharmacist identify if the patient has any risk factors which means they should not be given Maloff Protect.

- Pack Calculator
 - This will help the pharmacist calculate the number of tablets to supply depending on how long the patient is going to be travelling for.
- Pharmacist Checklist
 - The Pharmacist Checklist will remind the pharmacist of actions to take when supplying Maloff Protect.

The following additional resources will also be provided for patients:

- User Reminder Card
 - The User Reminder Card displays a daily calendar to help patients track or record whether they have taken their dose for that day.
 - The other side of the card has a space for the pharmacist to provide the address or directions to the nearest place to receive full travel advice (including advice other than on prevention of malaria).
- User Reminder App
 - The User Reminder App will allow patients to program a daily reminder on their phone to remind them to take Maloff Protect at a set time each day. The User Reminder App will be accessible through a QR code on the label.

6. What do you think?

- Maloff Protect is used in the prevention of malaria in adults travelling to areas where malaria is prevalent.
- Maloff Protect is only at the moment available on prescription.
- We propose to make it available in pharmacies.
- The MHRA considers that this product can be available as a Pharmacy medicine.
- We want to know what you think about this change.

Please tell us your views – please use the form on the next page in Annex 1. Please respond by 6 April 2017.

Ref:

Your details

Name:

Position (if applicable):

Organisation (if applicable):

Email:

1. Do you consider that Maloff Protect should be available as a Pharmacy medicine?

Yes No Not sure

Please provide any comments or evidence to support your response:

2. Do you have any specific comments on the leaflet or the label provided in the public reclassification report for Maloff Protect?

3. Do you have any other comments on the reclassification?

4. The MHRA may publish consultation responses. Do you want your response to remain confidential?

Yes Partially* No

*If partially, please indicate which parts you wish to remain confidential. In line with the Freedom of Information Act 2000, if we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. Responses to consultation will not normally be released under FOI until the regulatory process is complete.

Responses can be continued onto a separate page if required. This form should be returned by email (reclassification@mhra.gsi.gov.uk) to arrive by **6 April 2017**. Contributions received after that date cannot be included in the exercise.

Patient Information Leaflet

ANNEX 2

Label

ANNEX 3

Summary of Product Characteristics

ANNEX 4

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

Maloff Protect 250 mg/100 mg tablets

atovaquone/proguanil hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist or doctor if you need more information or advice.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What Maloff Protect is and what it is used for
2. What you need to know before you take Maloff Protect
3. How to take Maloff Protect
4. Possible side effects
5. How to store Maloff Protect
6. Contents of the pack and other information

1. WHAT MALOFF PROTECT IS AND WHAT IT IS USED FOR

Maloff Protect belongs to a group of medicines called antimalarials. It contains two active ingredients, atovaquone and proguanil hydrochloride.

Maloff Protect is used to prevent malaria. It is available from the pharmacy for adults. It is not suitable for use in children or adolescents unless it has been prescribed for them by a doctor. If you are under 18 and you are visiting an area where there is malaria, talk to your doctor, nurse or pharmacist for advice.

Malaria is spread by the bite of an infected mosquito, which passes the malaria parasite (*Plasmodium falciparum*) into the bloodstream. Maloff Protect prevents malaria by killing this parasite.

IMPORTANT: You must get advice from a healthcare professional about which antimalarial medicine or medicines to take. You must ask your doctor, nurse or pharmacist if Maloff Protect is suitable for the part of the world that you are visiting. **Getting advice for malaria is only one of the aspects to protect your health before your travel. Remember to seek a full travel consultation.**

Protect yourself from malaria

People of any age can get malaria. It is a serious disease, but it is preventable. As well as taking Maloff Protect, it is very important that you also take steps to avoid being bitten by mosquitoes. The bite avoidance measures listed below should be used in combination for maximum effectiveness.

- **Use insect repellent on exposed areas of the skin.**
- **Wear clothing that covers most of the body,** especially after sunset as this is the time when mosquitoes are most active.
- **Sleep in a room with screened windows and doors or under a mosquito net (it is preferable to sleep under a mosquito net treated with insecticide if possible).**
- **Close windows and doors at sunset,** if they are not screened.
- **Sleep in a room with air-conditioning or a fan,** as mosquitoes are less active in cooler temperatures.
- **Consider using an insecticide** (mats, spray, plug-ins) to clear a room of insects or to stop mosquitoes from entering the room.

If you need further advice, talk to your doctor or pharmacist.

It is still possible to get malaria after taking the necessary precautions. Some types of malaria infection take a long time to cause symptoms, so the illness may not start until several days, weeks or even months after returning from abroad.

See a doctor immediately if you get these symptoms, particularly within three months but even up to one year after returning home:

- a high temperature (fever)
- headache
- tiredness
- sweats and chills
- vomiting

Tell your doctor that you have visited a malaria area.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE MALOFF PROTECT

Do not take Maloff Protect if you:

- are allergic to atovaquone and/or proguanil hydrochloride or any of the ingredients of this medicine (listed in section 6)
- have kidney disease
- have liver disease

Do not take Maloff Protect unless it has been prescribed for you by a doctor or other qualified prescriber if you:

- are breastfeeding, pregnant or think you may be pregnant (see section 'Pregnancy and Breastfeeding')
- are under 18 years old or weigh less than 40 kg
- have ever had **epilepsy**, convulsions or fits
- suffer from **depression**
- have tuberculosis

Do not take Maloff Protect if you are already taking any of the following medicines:

- etoposide, used to treat cancer
- metoclopramide, used to treat nausea and vomiting
- the antibiotics tetracycline, rifampicin or rifabutin
- indinavir, efavirenz, zidovudine or certain medicines called protease inhibitors, used to treat human immunodeficiency virus (HIV)
- warfarin, other coumarin based anticoagulants, or new oral anticoagulants (NOACs) such as dabigatran etexilate, rivaroxaban, and apixaban

Talk to your doctor or pharmacist for advice.

Warnings and precautions:

- If you are sick (*vomit*) **within one hour** of taking your Maloff Protect tablet, take another dose straight away. If you don't start vomiting until **more than one hour** after taking Maloff Protect, do not take another Maloff Protect tablet until your next dose is due, as it is likely that Maloff Protect will already be in your system
- It is very important to **take the full course** of Maloff Protect. If you have to take extra tablets due to sickness, you may need to get some more
- If you have been vomiting or have diarrhoea, it is especially important to use extra bite prevention, such as repellents and bed nets. The Maloff Protect you have taken may not be as effective because you may absorb less than you need

Tell your doctor or pharmacist if you have taken any medicines to prevent or treat malaria before and they have not worked or if you have had an allergic reaction to them. Maloff Protect may not be suitable for you.

Other medicines and Maloff Protect

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines that you buy without a prescription.

Do not take Maloff Protect if you are taking any of the medicines listed in the above section "Do not take Maloff Protect".

REMEMBER to tell your doctor or pharmacist if you start taking any other medicines while you're taking Maloff Protect.

Maloff Protect with food and drink

Take Maloff Protect with food or a milky drink, where possible. This will increase the amount of Maloff Protect your body can absorb, and make your treatment more effective.

It is best if you swallow the tablets whole and do not crush them.

Pregnancy and breastfeeding

If you are pregnant, think you may be pregnant or intend to get pregnant, or you are breastfeeding, do not take Maloff Protect unless your doctor tells you to.

Pregnant women have an increased risk of developing severe malaria and a higher risk of fatality compared to non-pregnant women.

Seek advice from your doctor or pharmacist if you are pregnant or breastfeeding and need to take an antimalarial.

Driving and using machines

Maloff Protect makes some people feel dizzy. If you feel dizzy, do not drive, use machines or take part in activities where you may put yourself or others at risk.

(Please turn over)

3. HOW TO TAKE MALOFF PROTECT

Always take this medicine exactly as described in this leaflet or as your doctor, nurse or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Take Maloff Protect with food or a milky drink, where possible as this helps your body absorb the active ingredients.

It is best to take Maloff Protect at the **same time each day**.

Adults: Take one tablet once a day, as described below.

- Start taking Maloff Protect one to two days before travelling to an area which has malaria.
- Continue taking it every day during your stay.
- Take Maloff Protect for another seven days after your return to a malaria-free area.
- Take the full course of Maloff Protect for maximum protection. Stopping early puts you at risk of getting malaria, as it takes seven days to ensure that any parasites that may be in your blood after a bite from an infected mosquito are killed.

Maloff Protect is only available without a prescription for adults. It is not suitable for use in children or adolescents unless it has been prescribed for them by a doctor. If you are under 18 and you are visiting an area where there is malaria, talk to your doctor, nurse or pharmacist for advice.

If you take more Maloff Protect than you should

Contact a doctor or pharmacist for advice. If possible, show them the Maloff Protect pack.

If you forget to take Maloff Protect

It is important that you take the full course of Maloff Protect. If you forget to take a dose, take your next dose as soon as you remember. Then continue your treatment as before.

Do not take a double dose (two doses at the same time) to make up for a missed dose.

Only take an additional dose if you are sick (vomit) within one hour of taking Maloff Protect. See "Warnings and precautions" overleaf.

Don't stop taking Maloff Protect unless your doctor or pharmacist tells you to. The only exception is if you experience one of the serious side effects listed in section 4 below.

Talk to your doctor or pharmacist if you need any advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Maloff Protect can cause side effects, although not everybody gets them.

IMPORTANT: If any side effect causes you to stop taking Maloff Protect, or if you vomit or have diarrhoea whilst taking Maloff Protect, you should continue to protect yourself against malaria as much as possible. Information on how to protect yourself from malaria is provided in section one of this leaflet. The bite avoidance measures listed in section one should be used in combination for maximum effectiveness.

Look out for the following severe reactions. They have occurred in a small number of people, but their exact frequency is unknown.

Stop taking Maloff Protect and contact a doctor immediately if you notice any of the following symptoms:

- **Severe allergic reactions** - signs include:
 - rash and itching
 - sudden wheezing, tightness of the chest or throat, or difficulty breathing
 - swollen eyelids, face, lips, tongue or other part of the body
- **Severe skin reactions:**
 - skin rash, which may blister and looks like small targets (central dark spots, surrounded by paler area with a dark ring around the edge) (erythema multiforme)
 - severe widespread rash with blisters and peeling skin, particularly occurring around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)

Most of the following side effects reported have been mild and have not lasted very long.

Very common: may affect more than 1 in 10 people

- headache
- feeling sick and being sick (nausea and vomiting)
- stomach pain
- diarrhoea

Common: may affect up to 1 in 10 people

- dizziness
- sleeping problems (insomnia)
- strange dreams
- depression
- loss of appetite
- fever
- rash
- cough
- allergic reactions
- itching (pruritus)

Common side effects, which may show up in your blood tests are:

- reduced numbers of red blood cells (anaemia) which can cause tiredness, headaches and shortness of breath

- reduced numbers of white blood cells (neutropenia) which may make you more likely to catch infections
- low levels of sodium in the blood (hyponatraemia)
- an increase in liver enzymes

Uncommon: may affect up to 1 to 100 people

- anxiety
- an unusual awareness of abnormal beating of the heart (palpitations)
- swelling and redness of the mouth
- red swollen patches on the skin (hives)
- hair loss

Uncommon side effects that may show up in your blood tests:

- an increase in amylase (an enzyme produced in the pancreas)

Rare: may affect up to 1 in 1,000 people

- seeing or hearing things that are not there (hallucinations)

Other side effects:

Other side effects have occurred in a small number of people but their exact frequency is unknown.

- pancytopenia (a decrease in all types of blood cells)
- inflammation of the liver (hepatitis)
- blockage of the bile ducts (cholestasis)
- increase in heart rate (tachycardia)
- inflammation of the blood vessels (vasculitis) which may be visible as red or purple raised spots on the skin but can affect other parts of the body
- fits (seizures)
- panic attacks, crying
- nightmares
- severe mental health problem in which the person loses contact with reality and is unable to think and judge clearly
- mouth ulcers
- blisters
- peeling skin
- increased sensitivity of the skin to sunlight
- effects on your stomach (gastric intolerance)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE MALOFF PROTECT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Maloff Protect contains

The active substances are atovaquone and proguanil hydrochloride. Each tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride.

The other ingredients are:

Core

Poloxamer 188, Microcrystalline Cellulose, Low-substituted Hydroxypropyl Cellulose, Povidone K30, Sodium Starch Glycolate Type A, Silica Colloidal anhydrous, Magnesium Stearate

Coating

Hypromellose, Titanium Dioxide (E171), Iron Oxide Red (E172), Macrogol 400, Macrogol 8000

What Maloff Protect looks like and contents of the pack

Maloff Protect tablets are 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.

Maloff Protect tablets are supplied in PVC/PVDC (clear) and hard tempered PVC/PVDC-Aluminium foil blisters containing 12 tablets.

Pack size: 24 or 36 tablets

Marketing Authorisation Holder

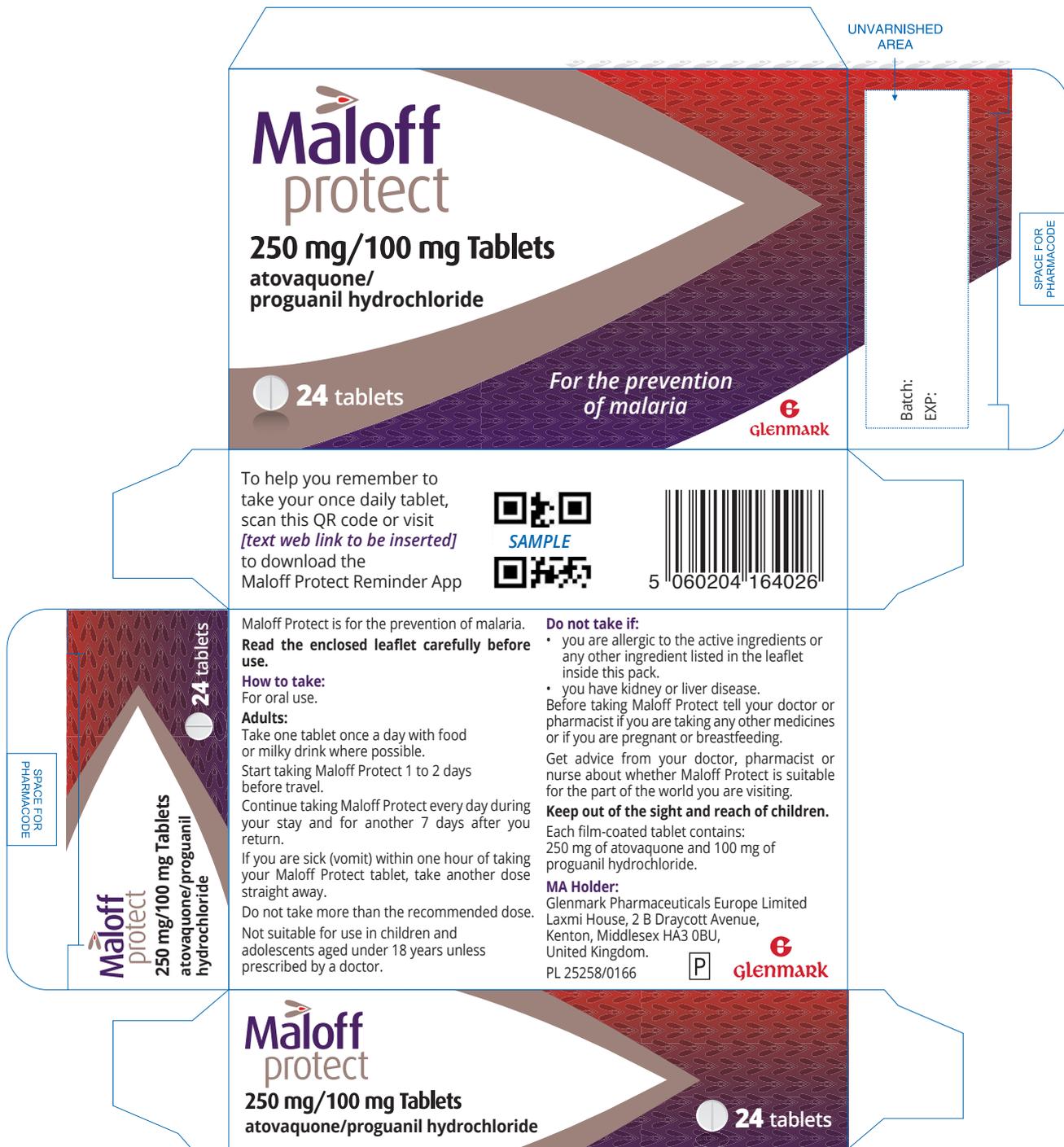
Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2 B Draycott Avenue,
Kenton, Middlesex, HA3 0BU,
United Kingdom

Manufacturer

Glenmark Pharmaceuticals Europe Limited.
Building 2, Croxley Green Business Park, Croxley Green, Hertfordshire, WD18 8YA, United Kingdom
Glenmark Pharmaceuticals s.r.o.
Hvězdova 1716/2b, 140 78 Prague 4,
Czech Republic

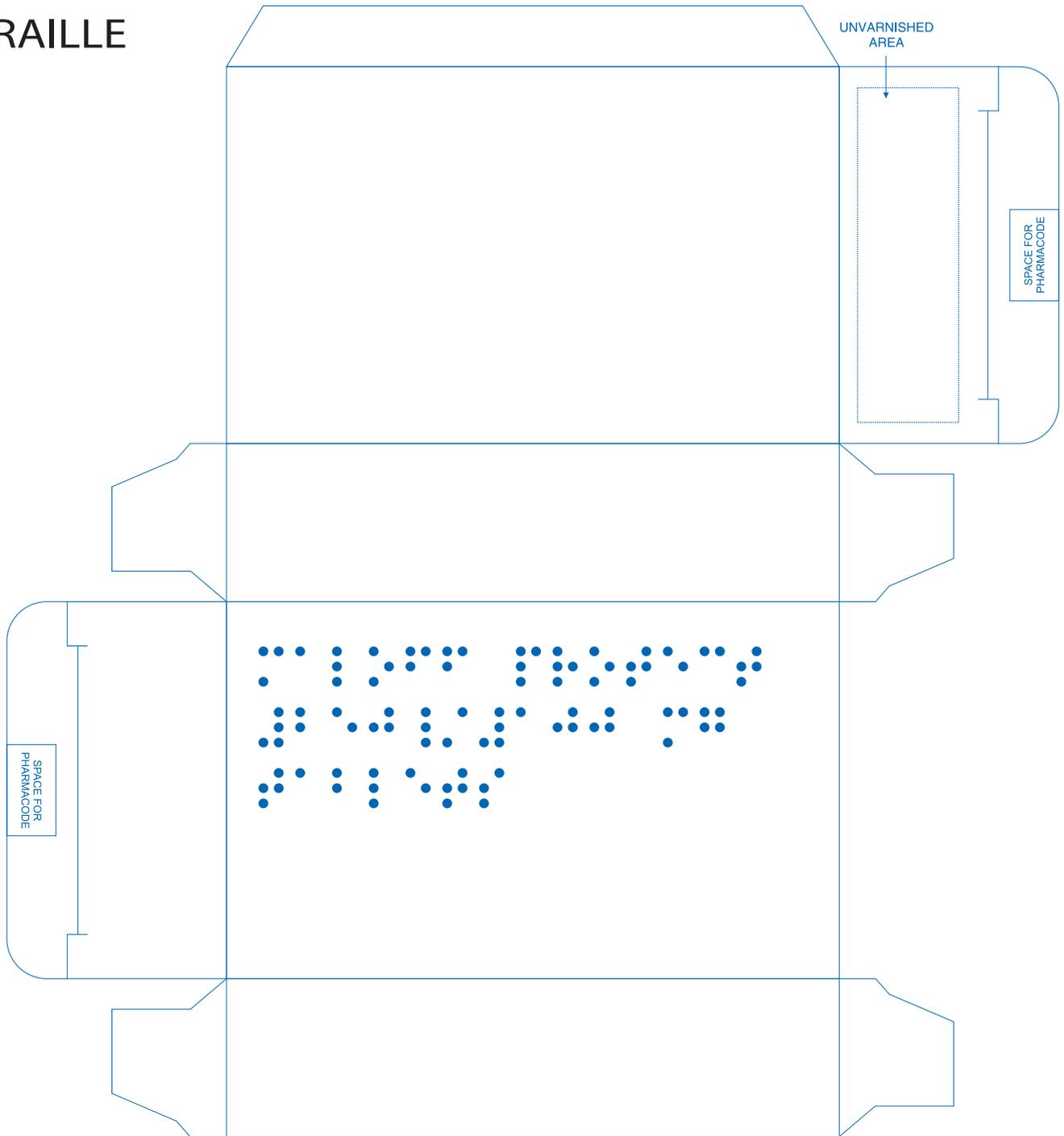
Tillomed Laboratories Limited
3 Howard Road, Eaton Socon,
St. Neots, Cambridgeshire, PE19 8ET,
United Kingdom

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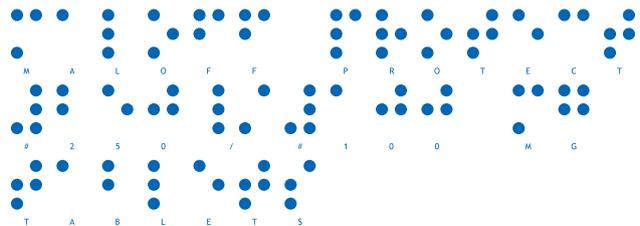




BRAILLE



Braille reads: Maloff Protect
(numeral sign) 250 mg/
(numeral sign) 100 mg
tablets



SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Maloff Protect 250 mg/100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Maloff Protect tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets (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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for:

- Chemoprophylaxis of *Plasmodium falciparum* (*P. Falciparum*) malaria in adults.

Because Maloff Protect is effective against drug sensitive and drug resistant *P. falciparum* it is especially recommended for chemoprophylaxis of *P. falciparum* malaria where the pathogen may be resistant to other antimalarials.

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.

4.2 Posology and method of administration

Method of administration

The daily dose should be taken with food or a milky drink (to ensure maximum absorption) at the same time each day.

The tablets should preferably not be crushed.

If patients are unable to tolerate food, Maloff Protect should be administered, but systemic exposure of atovaquone will be reduced. In the event of vomiting within one hour of dosing a repeat dose should be taken.

Posology

Chemoprophylaxis

Chemoprophylaxis should:

- commence one to two days prior to entering a malaria-endemic area, continue during the period of the stay,
- continue for seven days after leaving the area.

In residents (semi-immune subjects) of endemic areas, the safety and effectiveness of Maloff Protect has been established in studies of up to 12 weeks.

In non-immune subjects, the average duration of exposure in clinical studies was 27 days.

Dosage in adults

One Maloff Protect tablet daily.

Maloff Protect tablets are not recommended for malaria chemoprophylaxis in persons under 40 kg bodyweight.

Dosage in the elderly

A pharmacokinetic study indicates that no dosage adjustments are needed in the elderly (see Section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Patients with diagnosed renal impairment of any severity
- Patients with diagnosed hepatic impairment of any severity.
- Maloff Protect is contraindicated for use in children and adolescents

4.4 Special warnings and precautions for use

Persons taking Maloff Protect for chemoprophylaxis of malaria should be advised to take a repeat dose if they vomit within one hour of dosing. In the event of diarrhoea, 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 in clinical trials of Maloff Protect for malaria chemoprophylaxis. However, as with other antimalarial agents, subjects with diarrhoea or vomiting should be advised to continue with malaria prevention measures by complying with personal protection measures (repellents, bed nets).

Occasionally, severe allergic reactions (including anaphylaxis) have been reported in patients taking Maloff Protect. If patients experience an allergic reaction (see section 4.8) Maloff Protect should be discontinued promptly and appropriate treatment initiated.

Maloff Protect should not be used unless advised by a doctor or other qualified prescriber:

- In patients who are taking etoposide. (see section 4.5)
- In patients who are taking rifampicin or rifabutin (see section 4.5)
- In patients taking metoclopramide (see section 4.5)
- In patients taking warfarin or other oral anticoagulant (see section 4.5)

- In patients who are taking tetracycline (see section 4.5)
- In patients who are taking indinavir, efavirenz, zidovudine or boosted protease inhibitors (see section 4.5)
- In patients with a history of depression or seizures
- In patients with tuberculosis
- Patients who are pregnant, planning to become pregnant or breastfeeding. Pregnant women have an increased risk of developing severe malaria and a higher risk of fatality compared to non-pregnant women.

The safety and effectiveness of Maloff Protect has not been established for chemoprophylaxis of malaria in patients who weigh less than 40 kg.

Travellers should be reminded the need of receiving a full travel consultation if they have not already done so to undertake an overall risk assessment-based package of travel health advice. Malaria prophylaxis is only one of the aspects of pre-travel advice.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of rifampicin or rifabutin with Maloff Protect is not recommended as it is known to reduce plasma concentrations of atovaquone levels by approximately 50% and 34%, respectively (see section 4.4).

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 by as much as 75%. This combination should be avoided whenever possible (see section 4.4).

Proguanil may potentiate the effect of warfarin and other coumarin based anticoagulants which may lead to an increase in risk of haemorrhage. The mechanism of this potential drug interaction has not been established. Caution is advised when initiating or withdrawing malaria prophylaxis with atovaquone proguanil in patients on continuous treatment with oral anticoagulants. The dose of oral anticoagulant may need to be adjusted during Maloff

Protect use or after its withdrawal, based on INR results. Concomitant treatment with warfarin, other coumarin-based anticoagulants, or NOACs such as dabigatran etexilate, rivaroxaban, and apixaban should be undertaken with caution. (see section 4.4) Apixaban and rivaroxaban are substrates of CYP3A4 and p-glycoprotein, whilst dabigatran is a substrate of p-glycoprotein. Atovaquone may produce minor inhibition of CYP3A4, but the effect of proguanil on this enzyme is unknown. Neither atovaquone nor proguanil inhibits p-glycoprotein.

Concomitant treatment with tetracycline has been associated with decreases in plasma concentrations (AUC) of atovaquone. (see section 4.4)

Concomitant administration of atovaquone and indinavir results in a decrease in the minimum concentration after dosing (C_{\min}) of indinavir (23% decrease; 90% CI 8-35%). (see section 4.4)

The co-administration of atovaquone at doses of 45 mg/kg/day in children (n=9) with acute lymphoblastic leukaemia for chemoprophylaxis of pneumocystis pneumonia (PCP) was found to increase the AUC of etoposide and its metabolite etoposide catechol by a median of 8.6% (P=0.055) and 28.4% (P=0.031) (respectively compared to the co-administration of etoposide

and sulfamethoxazole-trimethoprim). Caution should be advised in patients receiving concomitant therapy with etoposide (see section 4.4).

Pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a concomitant course of Maloff Protect would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine.

Proguanil is primarily metabolised by CYP2C19. However, potential pharmacokinetic interactions with other substrates, inhibitors (e.g. moclobemide, fluvoxamine) or inducers (e.g. artemisinin, carbamazepine) of CYP2C19 are unknown (see section 5.2).

Atovaquone is highly protein bound (>99%) but does not displace other highly protein bound drugs *in vitro*, indicating significant drug interactions arising from displacement are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of atovaquone and proguanil hydrochloride when administered concurrently for use in human pregnancy has not been established and the potential risk is unknown.

Animal studies showed no evidence for teratogenicity of the combination. The individual components have shown no effects on parturition or pre- and post-natal development. Maternal toxicity was seen in pregnant rabbits during a teratogenicity study (see section 5.3).

The proguanil component of Maloff Protect acts by inhibiting parasitic dihydrofolate reductase. There are no clinical data indicating that folate supplementation diminishes drug efficacy.

Lactation

The atovaquone concentrations in milk, in a rat study, were 30% of the concurrent atovaquone concentrations in maternal plasma. It is not known whether atovaquone is excreted in human milk.

Proguanil is excreted in human milk in small quantities.

Maloff Protect should not be used by women who are breastfeeding unless advised by a doctor or other qualified prescriber.

4.7 Effects on ability to drive and use machines

Dizziness has been reported. Patients should be warned that if affected they should not drive, operate machinery or take part in activities where this may put themselves or others at risk.

4.8 Undesirable effects

In clinical trials of atovaquone/proguanil in the treatment of malaria the most commonly reported adverse reactions were abdominal pain, headache, anorexia, nausea, vomiting, diarrhoea and coughing.

In clinical trials of atovaquone/proguanil for chemoprophylaxis of malaria, the most commonly reported adverse reactions were headache, abdominal pain and diarrhoea.

The following table provides a summary of adverse reactions that have been reported to have a suspected (at least possible) causal relationship to treatment with atovaquone/proguanil, in clinical trials and spontaneous post-marketing reports. The following convention is used for the classification of frequency:

very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); not known (cannot be estimated from the available data)

There are limited long term safety data in children. In particular, the long-term effects of Maloff Protect on growth, puberty and general development have not been studied.

System Organ Class	Very Common	Common	Uncommon	Rare	Not known²
Blood and lymphatic disorders		Anaemia Neutropenia ¹			Pancytopenia in patients with severe renal impairment ³
Immune system disorders		Allergic reactions			Angioedema ³ Anaphylaxis (see section 4.4) Vasculitis ³
Metabolism and nutrition disorders		Hyponatraemia ¹ Anorexia	Elevated amylase levels ¹		
Psychiatric disorders		Abnormal dreams Depression	Anxiety	Hallucinations (observed from spontaneous post marketing reports)	Panic attack Crying Nightmares Psychotic disorder
Nervous system disorders	Headache	Insomnia Dizziness			Seizure
Cardiac disorders			Palpitations		Tachycardia
Gastrointestinal disorders	Nausea ¹ Vomiting Diarrhoea Abdominal pain		Stomatitis		Gastric intolerance ³ Oral ulceration ³

System Organ Class	Very Common	Common	Uncommon	Rare	Not known ²
Hepatobiliary disorders		Elevated liver enzymes ^{1,4}			Hepatitis Cholestasis ³
Skin and subcutaneous tissue disorders		Pruritus Rash	Hair loss Urticaria		Stevens-Johnson syndrome Erythema multiforme Blister ² Skin exfoliation Photosensitivity reactions
General disorders and administration site conditions		Fever			
Respiratory, thoracic and mediastinal disorders		Cough			

1. Frequency taken from atovaquone label. Patients participating in clinical trials with atovaquone have received higher doses and have often had complications of advanced Human Immunodeficiency Virus (HIV) disease. Therefore, the causal relationship between the adverse experiences and atovaquone is difficult to evaluate. These events may have been seen at a lower frequency or not at all in clinical trials with atovaquone/proguanil.

2. Observed from post-marketing spontaneous reports. The frequency is unknown.

3. Observed with proguanil.

4. Clinical trial data for atovaquone/proguanil indicated that abnormalities in liver function tests were reversible and not associated with untoward clinical events.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

There is insufficient experience to predict the consequences or suggest specific management of Maloff Protect overdose. However, in the reported cases of atovaquone overdose, the observed effects were consistent with known undesirable effects of the drug. If overdose occurs, the patient should be monitored and standard supportive treatment applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIMALARIALS, Biguanides, Proguanil, combinations ATC Code: P01BB51

Maloff Protect is a fixed dose combination of atovaquone and proguanil hydrochloride which acts as a blood schizonticide and also has activity against hepatic schizonts of *P. falciparum*.

Mode of action

The constituents of Maloff Protect, 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 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. Proguanil also has antimalarial activity independent of its metabolism to cycloguanil, and proguanil, but not cycloguanil, is able to potentiate the ability of atovaquone to collapse mitochondrial membrane potential in malaria parasites. This latter mechanism may explain the synergy seen when atovaquone and proguanil are used in combination.

Microbiology

Atovaquone has potent activity against *Plasmodium* spp (*in vitro* half minimal inhibitory concentration [IC₅₀] against *P. falciparum* 0.23-1.43 ng/mL).

Atovaquone is not cross-resistant with any other antimalarial drugs in current use.

Among more than 30 *P. falciparum* isolates, *in vitro* resistance was detected against chloroquine (41% of isolates), quinine (32% of isolates), mefloquine (29% of isolates), and halofantrine (48% of isolates) but not atovaquone (0% of isolates).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC₅₀ against various *P. falciparum* strains of 4-20 ng/mL; some activity of proguanil and another metabolite, 4-chlorophenylbiguanide, is seen *in vitro* at 600-3000 ng/mL).

Atovaquone/proguanil acts as a blood schizonticide and also as activity against hepatic schizonts of *P. falciparum* that are resistant to other antimalarials, e.g. chloroquine, halofantrine, mefloquine, amodiaquine, and chloroquine + pyrimethamide/sulfadoxine.

In vitro studies of *P. falciparum* the combination of atovaquone and proguanil was shown to be synergistic. This enhanced efficacy was also demonstrated in clinical studies in both immune and non-immune patients.

5.2 Pharmacokinetic properties

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose. In clinical trials, where children have received Maloff Protect dosed by bodyweight, trough levels of atovaquone, proguanil and cycloguanil in children are generally within the range observed in adults.

Absorption

Atovaquone is a highly lipophilic compound with low aqueous solubility. The pharmacokinetics of atovaquone is similar for healthy subjects and HIV-infected patients. There is no bioavailability data for healthy subjects. In HIV-infected patients, the absolute bioavailability of a 750 mg single dose of atovaquone tablets taken with food is 23% with an inter-subject variability of about 45%.

Dietary fat taken with atovaquone increases the rate and extent of absorption, increasing AUC 2 to 3 times and C_{max} 5 times over fasting. Patients are recommended to take Maloff Protect tablets with food or a milky drink (see section 4.2).

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

Distribution

Apparent volume of distribution of atovaquone and proguanil is a function of bodyweight.

Atovaquone is highly protein bound (>99%) but does not displace other highly protein bound drugs *in vitro*, indicating that significant drug interactions arising from displacement are unlikely.

Following oral administration, the volume of distribution of atovaquone in adults and children is approximately 8.8 L/kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults and children ranged from 20 to 42 L/kg.

In human plasma the binding of atovaquone and proguanil was unaffected by the presence of the other.

Biotransformation

There is no evidence that atovaquone is metabolised and there is negligible excretion of atovaquone in urine with the parent drug being predominantly ($\geq 90\%$) eliminated unchanged in faeces.

Proguanil hydrochloride is partially metabolised, primarily by the polymorphic cytochrome P450 isoenzyme 2C19, with less than 40% being excreted unchanged in the urine. Its metabolites, cycloguanil and 4-chlorophenylbiguanide, are also excreted in the urine.

During administration of Maloff Protect at recommended doses, proguanil metabolism status appears to have no implications for treatment or chemoprophylaxis of malaria.

Elimination

The elimination half life of atovaquone is about 2-3 days in adults and 1-2 days in children.

The elimination half lives of proguanil and cycloguanil are about 12-15 hours in both adults and children.

Oral clearance for atovaquone and proguanil increases with increased bodyweight and is about 70% higher in an 80 kg subject relative to a 40 kg subject. The mean oral clearance in paediatric and adult patients weighing 10 to 80 kg ranged from 0.8 to 10.8 L/h for atovaquone and from 15 to 106 L/h for proguanil.

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 the young patients (AUC is increased by

140% and C_{\max} is increased by 80%), but there is no clinically significant change in its elimination half life (see section 4.2).

Pharmacokinetics in renal impairment

In adult 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. There are no studies in children with renal impairment.

Atovaquone C_{\max} and AUC are reduced by 64% and 54%, respectively, in patients with severe renal impairment.

In patients with severe renal impairment, the elimination half lives ($t_{1/2}$) for proguanil ($t_{1/2}$ 39 h) and cycloguanil ($t_{1/2}$ 37 h) are prolonged, resulting in the potential for drug accumulation with repeated dosing .

Pharmacokinetics in hepatic impairment

In adult patients with mild to moderate hepatic impairment there is no clinically significant change in exposure to atovaquone when compared to healthy patients. There are no studies in children with hepatic impairment.

In patients with mild to moderate hepatic impairment there is an 85% increase in proguanil AUC with no change in elimination half life and there is a 65-68% decrease in C_{\max} and AUC for cycloguanil.

No data are available in patients with severe hepatic impairment .

5.3 Preclinical safety data

Repeat dose toxicity:

Findings in repeat dose toxicity studies with atovaquone/proguanil hydrochloride combination were entirely proguanil related and were observed at doses providing no significant margin of exposure in comparison with the expected clinical exposure. As proguanil has been used extensively and safely in the treatment and chemoprophylaxis of malaria at doses similar to those used in the combination, these findings are considered of little relevance to the clinical situation.

Reproductive toxicity studies:

In rats and rabbits there was no evidence of teratogenicity for the combination. No data are available regarding the effects of the combination on fertility or pre- and post-natal development, but studies on the individual components of Maloff Protect have shown no effects on these parameters. In a rabbit teratogenicity study using the combination, unexplained maternal toxicity was found at a systemic exposure similar to that observed in humans following clinical use.

Mutagenicity:

A wide range of mutagenicity tests have shown no evidence that atovaquone or proguanil have mutagenic activity as single agents.

Mutagenicity studies have not been performed with atovaquone in combination with proguanil.

Cycloguanil, the active metabolite of proguanil, was also negative in the Ames test, but was positive in the Mouse Lymphoma assay and the Mouse Micronucleus assay. These positive

effects with cycloguanil (a dihydrofolate antagonist) were significantly reduced or abolished with folic acid supplementation.

Carcinogenicity:

Oncogenicity studies of atovaquone alone in mice showed an increased incidence of hepatocellular adenomas and carcinomas. No such findings were observed in rats and mutagenicity tests were negative. These findings appear to be due to the inherent susceptibility of mice to atovaquone and are considered of no relevance in the clinical situation.

Oncogenicity studies on proguanil alone showed no evidence of carcinogenicity in rats and mice.

Oncogenicity studies on proguanil in combination with atovaquone have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Poloxamer 188

Microcrystalline Cellulose

Low-substituted Hydroxypropyl Cellulose

Povidone K30

Sodium Starch Glycolate Type A

Silica colloidal anhydrous

Magnesium Stearate

Coating

Hypromellose

Titanium Dioxide E171

Iron Oxide Red E172

Macrogol 400

Macrogol 8000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/PVDC (clear) and hard tempered PVC/PVDC-Aluminium foil blisters containing 12 tablets.

Pack size: 24 or 36 tablets

6.6 Special precautions for disposal

7 MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Europe Limited,
Laxmi House, 2 B Draycott Avenue,
Kenton, Middlesex, HA3 0BU,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0166

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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