SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atovaquone Glenmark 750 mg/5 ml oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of suspension contains 150 mg atovaquone.

A unit dose of 5 ml contains 750 mg atovaquone.

Excipient with known effect: Each 5ml of oral suspension contains 50.00 mg benzyl alcohol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.

Atovaquone Glenmark 750 mg/5 ml oral suspension is a bright yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atovaquone Glenmark 750 mg/5 ml oral suspension is indicated for:

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] $\leq$ 45 mmHg (6 kPa) and oxygen tension in arterial blood (PaO2) $\geq$ 60 mmHg (8 kPa) breathing room air) in patients who are intolerant of co-trimoxazole therapy (see section 4.4).

4.2 Posology and method of administration

Posology

The importance of taking the full prescribed dose of Atovaquone Glenmark 750 mg/5 ml oral suspension with food should be stressed to patients. The presence of food, particularly high fat food, increases bioavailability two to three fold.

Dosage in adults
Pneumocystis pneumonia:
The recommended oral dose is 750 mg twice a day (1 x 5 ml morning and evening) administered with food each day for 21 days.

Higher doses may be more effective in some patients (see section 5.2).

Dosage in Children
Clinical efficacy has not been studied.

Dosage in Older people
There have been no studies of Atovaquone Glenmark 750 mg/5 ml oral suspension in the elderly (see section 4.4).

Renal or hepatic impairment
Atovaquone Glenmark 750 mg/5 ml oral suspension has not been specifically studied in patients with significant hepatic or renal impairment (see section 5.2 for pharmacokinetics in adults). If it is necessary to treat such patients with Atovaquone Glenmark 750 mg/5 ml oral suspension, caution is advised and administration should be closely monitored. Atovaquone Glenmark contains benzyl alcohol (see section 4.4).

4.3 Contraindications

Atovaquone is contra-indicated in individuals with known hypersensitivity to atovaquone or to any of the excipients listed in section 6.1.

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 Atovaquone Glenmark 750 mg/5 ml oral suspension with food.

Patients receiving concurrent tetracycline should be closely monitored (see section 4.5).

The concomitant administration of atovaquone and efavirenz or boosted protease-inhibitors should be avoided whenever possible (see section 4.5).

The concomitant administration of atovaquone and rifampicin or rifabutin is not recommended (see section 4.5).

Concurrent use of metoclopramide is not recommended. Another antiemetic treatment should be given (see section 4.5).

Atovaquone can increase the levels of etoposide and its metabolite (see section 4.5).

The efficacy of Atovaquone Glenmark 750 mg/5 ml oral suspension has not been systematically evaluated i) in patients failing other PCP therapy, including co-trimoxazole, ii) for treatment of severe episodes of PCP [(A-a) DO_2 > 45 mmHg (6kPa)], iii) as a prophylactic agent for PCP, or iv) versus intravenous pentamidine for treatment of PCP.

No data are available in non-HIV immuno-compromised patients suffering with PCP.

No clinical experience of atovaquone treatment has been gained in elderly patients. Therefore use in the elderly should be closely monitored.

Patients with pulmonary disease should be carefully evaluated for causes of disease other than PCP and treated with additional agents as appropriate. Atovaquone Glenmark 750 mg/5 ml oral suspension is not expected to be effective therapy for other fungal, bacterial, mycobacterial or viral diseases.

Benzyl alcohol
Atovaquone Glenmark contains benzyl alcohol which may cause allergic reactions.

Benzyl alcohol is associated with the risk of accumulation in newborn babies (up to 4 weeks old) due to metabolic immaturity. Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known.

Should not be used for more than a week in young children (less than 3 years old) due to increased risk of accumulation.
Should be used with caution and only if necessary, especially in pregnant or breast-feeding patients or in patients with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

Sodium
This medicine contains less than 1 mmol sodium (23 mg) in each 5 ml, that is to say essentially 'sodium free'.

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.

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, (see section 4.4).

Concomitant treatment with metoclopramide has been associated with a significant decrease (about 50%) in plasma concentrations of atovaquone (see section 4.4).Another antiemetic treatment should be given.

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 (see section 4.4).

Concomitant treatment with tetracycline has been associated with decreases in plasma concentrations of atovaquone.

The co-administration of atovaquone at doses of 45 mg/kg/day in children (n=9) with acute lymphoblastic leukaemia for prophylaxis of PCP was found to increase the plasma concentrations (AUC) of etoposide and its metabolite etoposide catechol by a median of 8.6% and 28.4% (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).

In clinical trials of Atovaquone Glenmark 750 mg/5 ml oral suspension 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.

Clinical trials have evaluated the interaction of Atovaquone Glenmark 750 mg/5 ml oral suspension Tablets with:

Zidovudine - Zidovudine does not appear to affect the pharmacokinetics of atovaquone. However, 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 three week, concomitant course of Atovaquone Glenmark 750 mg/5 ml oral suspension for the treatment of acute PCP would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine.

Didanosine (ddI) - ddI does not affect the pharmacokinetics of atovaquone as determined in a prospective multidose drug interaction study of atovaquone and ddI. However, there was a 24% decrease in the AUC for ddI when co-administered with atovaquone which is unlikely to be of clinical significance.

Nevertheless, the modes of interaction being unknown, the effects of atovaquone administration on zidovudine and ddI may be greater with atovaquone suspension. The higher concentrations of atovaquone possible with the suspension might induce greater changes in the AUC values for zidovudine or ddI than those observed. Patients receiving atovaquone and zidovudine should be regularly monitored for zidovudine associated adverse effects.

Concomitant administration of Atovaquone Glenmark 750 mg/5 ml oral suspension and indinavir results in a significant decrease in the Cmin of indinavir (23% decrease; 90% CI 8-35%) and the AUC (9% decrease; 90% CI 1-18%). Caution should be exercised on the potential risk of failure of indinavir treatment if co-administered with atovaquone.

In clinical trials of Atovaquone Glenmark 750 mg/5 ml oral suspension the following medications were not associated with a change in steady state plasma concentrations of atovaquone: fluconazole, clotrimazole, ketoconazole, antacids, systemic corticosteroids, non-steroidal anti-inflammatory drugs, anti-emetics (excluding metoclopramide) and H2-antagonists.

Atovaquone is highly bound to plasma proteins and caution should be used when administering Atovaquone Glenmark 750 mg/5 ml oral suspension concurrently with other highly plasma protein bound drugs with narrow therapeutic indices. Atovaquone does not affect the pharmacokinetics, metabolism or extent of protein binding of phenytoin in vivo. In vitro there is no plasma protein binding interaction between atovaquone and quinine, phenytoin, warfarin, sulfamethoxazole, indometacin or diazepam.

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. Atovaquone Glenmark contains benzyl alcohol (see section 4.4).

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. Atovaquone Glenmark contains benzyl alcohol (see section 4.4).

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of Atovaquone Glenmark 750 mg/5 ml oral suspension on driving performance or the ability to operate machinery

but a detrimental effect on such activities is not predicted from the pharmacology of the drug.

4.8 Undesirable effects

Patients participating in clinical trials with atovaquone have often experienced undesirable effects consistent with the course of advanced Human Immunodeficiency Virus (HIV) disease or of concomitant therapy. The following adverse reactions have been observed and reported to have a suspected (at least possible) causal relationship to treatment with atovaquone with the following frequencies:

The following convention is used for frequencies: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Common: anaemia, neutropenia

Metabolism and nutrition disorders

Common: hyponatraemia

Psychiatric disorders

Common: insomnia

Nervous system disorders

Common: headache

Gastrointestinal disorders

Very common: nausea

Common: diarrhoea, vomiting

Hepatobiliary disorders

Common: elevated liver enzymes levels

Immune System Disorders

Common: hypersensitivity reactions including angioedema, bronchospasm and throat tightness

Skin and subcutaneous tissue disorders

Very common: rash, pruritus

Common: urticaria

Not known: erythema multiforme, Stevens-Johnson Syndrome

General disorders and administration site conditions

Common: fever

Investigations

Uncommon: elevated amylase levels

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, ATC Code: P01A X06.

Mode of Action

Atovaquone is a selective and potent inhibitor of the eukaryotic mitochondrial electron transport chain in a number of parasitic protozoa and the parasitic fungus P. jiroveci. The site of action appears to be the cytochrome bc1 complex (complex III). The ultimate metabolic effect of such blockade is likely to be inhibition of nucleic acid and ATP synthesis.

Microbiology

Atovaquone has potent activity against Pneumocystic sp, both in vitro and in animal models, (IC50 0.5-8 µg/mL).

5.2 Pharmacokinetic properties

Absorption

Atovaquone is a highly lipophilic compound with a low aqueous solubility. It is 99.9% bound to plasma proteins. The bioavailability of the drug demonstrates a relative decrease with single doses above 750 mg, and shows considerable inter-individual variability. Average absolute bioavailablility of a 750 mg single dose of atovaquone suspension administered with food to adult HIV positive males is 47% (compared to 23% for Atovaquone Glenmark 750 mg/5 ml oral suspension tablets). Following the intravenous administration, the volume of distribution and clearance were calculated to be 0.62±0.19 l/kg and 0.15±0.09 ml/min/kg, respectively.

The bioavailability of atovaquone is greater when administered with food than in the fasting state. In healthy volunteers, a standardized breakfast (23 g fat; 610 kCal) increased bioavailability two to three-fold following a single 750 mg dose. The mean area under the atovaquone plasma concentration-time curve (AUC) was increased 2.5 fold and the mean Cmax was increased 3.4 fold. The mean (±SD) AUC values for suspension were 324.3 (±115.0) µg/ml.h fasted and 800.6 (±319.8) µg/ml.h with food.

In a safety and pharmacokinetic study in patients with PCP, the following results were obtained:

Dose regimen	750 mg twice daily	1000 mg twice daily
Number of Patients	18	9
C avg, ss (range)	22 µg/ml (6-41)	25.7 µg/ml (15-36)
% of patients with C avg, ss >15 µg/ml	67%	100%

In a small safety and pharmacokinetic study of two higher dosing regimens [750 mg three times daily (n=8) and 1500 mg twice daily (n=8)] in HIV infected volunteers with severity criteria comparable to patients with PCP, similar Cavg were reached with the two doses [for the 750 mg tid and 1500 mg bid doses: 24.8 (7-40) and 23.4 µg/ml (7-35) respectively]. Moreover, for both doses a Cavg, ss >15 µg/ml was reached in 87.5% of patients.

Average steady state concentrations above 15 µg/ml are predictive of a high (>90%) success rate.

In healthy volunteers and patients with AIDS, atovaquone has a half-life of 2 to 3 days.

Biotransformation/Elimination

In healthy volunteers there is no evidence that the drug is metabolised and there is negligible excretion of atovaquone in the urine, with parent drug being predominantly (>90%) excreted unchanged in faeces.

5.3 Preclinical safety data

Carcinogenicity

Oncogenicity studies in mice showed an increased incidence of hepatocellular adenomas and carcinomas without determination of the no observed adverse effect level. 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 not predictive of a risk in the clinical situation.

Reproductive toxicity

In the dosage range of 600 to 1200 mg/kg studies in rabbits gave indications of maternal and embryotoxic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Xanthan Gum

Poloxamer 188

Hypromellose

Saccharin sodium dihydrate

Citric acid monohydrate

Sodium citrate dihydrate

Purified water

Tutti Frutti Flavour (051880 AP0551) containing flavouring substances, maize maltodextrin, propylene glycol and alpha-tocopherol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

After first opening, the suspension may be stored for up to 21 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Do not refrigerate or freeze.

6.5 Nature and contents of container

226 ml in a plastic bottle (HDPE) with child resistant closure (polypropylene).

A 5 ml measuring spoon (polypropylene) is included.

6.6 Special precautions for disposal

Do not dilute

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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