

## Atovaquone/ proguanil hydrochloride and psychotic disorder

### Introduction

Atovaquone/ proguanil hydrochloride (generic, Malarone<sup>®</sup> and Malarone<sup>®</sup> junior) is indicated for the prophylaxis of *Plasmodium falciparum* malaria in travelers (Malarone<sup>®</sup> junior: 11-40 kg) and for the treatment of acute and uncomplicated *Plasmodium falciparum* malaria (Malarone<sup>®</sup> junior: 5-11 kg) [1-7]. It is recommended for the prophylaxis and the treatment of *Plasmodium falciparum* in the area where the pathogen is resistant to other antimalarials [1-7].

Atovaquone/ proguanil interferes with two different pathways, both are involved in the biosynthesis of pyrimidines required for the nucleic acid replication of the malaria parasite. Atovaquone inhibits the mitochondrial electron transport and disrupts the mitochondrial membrane potential. The active metabolite of proguanil, cycloguanil, inhibits dihydrofolate reductase and enhances the effect of atovaquone on the mitochondrial membrane potential [1,2].

Atovaquone/ proguanil hydrochloride was granted marketing authorization in the Netherlands on 25 July 2000 (Malarone<sup>®</sup>) [1] and on 3 March 2003 (Malarone junior<sup>®</sup>) [2].

The term psychotic disorder has historically received a number of different definitions, none of which has achieved universal acceptance. The narrowest definition of psychotic disorder is restricted to symptoms like delusions or prominent hallucinations. A broader definition concerns a mental disorder that resulted in "impairment that grossly interferes with the capacity to meet ordinary demands of life". The term has been defined as a loss of ego boundaries or a gross impairment in reality testing [8].

### Reports

The Netherlands Pharmacovigilance Centre Lareb received four reports of psychotic disorder associated with atovaquone/ proguanil, in a period from June 1<sup>st</sup> 1995 to April 22<sup>th</sup> 2014, see Table 1. Additional information regarding the cases is described below.

Table 1. Reports of psychotic disorder associated with the use of atovaquone/ proguanil.

Patient, Sex, Age, source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 153871 M, 21-70 years Psychiatrist	Atovaquone/ proguanil tablet Malaria prophylaxis		Short psychotic disorder	2 days discontinued recovered in 3 months
B 36146 M, 41-50 years Community health professional	Atovaquone/ proguanil tablet Malaria prophylaxis	Chlorthalidone 25 mg and cetirizine 10 mg.	Strong psychosis with severe suicidal characteristics, irritability, ulcer hands, and paraesthesia of the mouth	1 day discontinued recovered in 2 days
C 56444 F 41-50 years Community health professional	Atovaquone/ proguanil tablet Malaria prophylaxis		Auditory hallucinations that ultimately resulted in a psychosis	12 days Discontinued Unknown
D 54661 F, unknown Physician	Atovaquone/ proguanil tablet Drug use for unknown indication		Psychosis	Unknown Unknown Recovered

In all four cases, it is unknown when the consumers started the use of atovaquone/ proguanil at home or abroad.

Casus A: The patient was hospitalized in the psychiatric ward and treated with olanzapine. Another influencing factor mentioned was sleep deprivation. The destination for holiday and medical history were unknown.

Casus B: The community health professional reported about himself. The patient was not able to continue atovaquone/ proguanil therapy and evacuation from Tanzania was necessary. Cetirizine was started 1 month before the start of atovaquone/ proguanil and withdrawn on the same date as atovaquone/ proguanil. There was no psychiatric history and he had never had atovaquone/ proguanil therapy before.

Casus C: The destination was unknown. The patient was admitted at a psychiatric hospital and diagnosed with Schizophrenia. There is no information on further treatment. Other influencing factor was a stressful period before administration of atovaquone/ proguanil.

Casus D: Due to psychosis the patient had returned back home from Africa.

## Other sources of information

### SmPC

All the SmPCs of atovaquone/ proguanil mention abnormal dreams, depression, anxiety, hallucinations, panic attack and nightmares as possible adverse drug reactions (ADRs) [1-4,6,7,9]. The SmPCs of brand Malarone<sup>®</sup> and Malarone<sup>®</sup> junior also mention psychiatric disorders [1,2]. Psychotic disorder is not explicitly mentioned in the SmPCs of atovaquone/ proguanil [1-4,6,7,9].

The US SmPC of the FDA mentions that psychotic events (such as hallucinations) have been identified during postmarketing use of atovaquone/ proguanil. However, a causal relationship has not been established [10].

### Literature

A search on Pubmed revealed no specific information of atovaquone/ proguanil induced psychotic disorder or hallucinations. One systematic review and meta-analysis, written by Halima Nakato *et al.* [11], described the occurrence of neuropsychiatric ADRs of atovaquone/ proguanil compared to chloroquine/ proguanil or mefloquine. Ten randomized controlled trials were included. Of these trials, three meta-analysis were included in which patients could report ADRs. No significant difference was found (RR = 0.74; 95% CI = 0.5 - 1.1; I<sup>2</sup> = 86.7%) in the reporting of neuropsychiatric ADRs. One of the included trials [12] described the neuropsychiatric ADRs of atovaquone/ proguanil compared to mefloquine in a randomized double blind study. The atovaquone/ proguanil group (n=493) experienced lower neuropsychiatric ADRs than the mefloquine group (n=483) (14% versus 29%, P = 0.001). Among the neuropsychiatric ADRs reported were dreaming, insomnia, anxiety and depression. No hallucination or psychotic disorder were reported. The study was funded by Glaxo Smith Kline.

### Databases

Table 2. Number of reported cases of psychotic disorder associated with the use of atovaquone/ proguanil in the database of Lareb, the WHO and Eudravigilance on April 23<sup>rd</sup> [13-15].

Drug	Number of reports	ROR (95% CI)
Atovaquone/ proguanil	Lareb: 4	4.4 (95% CI 1.6 – 12.0)

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October 2014

Drug	Number of reports	ROR (95% CI)
	WHO: 27	6.0 (95% CI 4.1 – 8.8)
	Eudravigilance: 29	9.0 (95% CI; 6.2 – 12.9)

## Prescription data

Prescription data are retrieved from the GIP database [16], where most of the reimbursed prescriptions are stored. Because atovaquone/ proguanil is not covered by most of the basic insurance, the numbers of patients in the GIP database are not a real reflection of the users of atovaquone/ proguanil. Therefore, prescription data are unknown.

## Mechanism

No possible mechanism explaining this association could be found in the literature. Atovaquone is a highly lipophilic compound. Intake with fat can increase the Area Under the Curve (AUC) by a factor 2 to 3 and the maximum concentration (C<sub>max</sub>) by a factor 5 compared to fasting. The bioavailability of atovaquone shows considerable interindividual variability of 45%. It is advised to administer atovaquone/ proguanil with food or a dairy drink to increase the degree of absorption [1]. Proguanil is not dependent on the food intake [1].

Theoretically, the possible high fat content of a traveler's diet in addition to the variable interindividual availability makes specific travelers group at risk to a higher concentration of atovaquone. It is plausible that a higher blood concentration increases the risk of ADRs. However, in susceptible air travel passengers, a jet lag may be sufficient to exacerbate affective illness and result in psychiatric morbidity [17].

No information could be found in literature about the passage of the drug through the blood-brain barrier.

## Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received four reports of psychotic disorder associated with the use of atovaquone/ proguanil. All reports were assessed as serious. In case A and C, the consumer was hospitalized in the psychiatric ward. Patient C was diagnosed with Schizophrenia at the age of 44. The onset of Schizophrenia typically occurs between the late teens and the mid-30s, but a late-onset (e.g., after age 45 years) may also occur. Women are more likely to have a later-onset [8].

In case B and D, evacuation to home country was necessary. The latency period ranged from 1 day to 12 days. Patient B had no psychiatric history before and had a positive dechallenge. The patient recovered 2 days after atovaquone/ proguanil and cetirizine were withdrawn. The SmPC of cetirizine describes also hallucinations and confusion with an incidence of 0.001-0.01% [18]. However, because cetirizine started a month earlier than atovaquone/ proguanil and the psychotic disorder occurred 1 day after the start of atovaquone/ proguanil, it is more likely that the patient recovered due to the withdrawal of atovaquone/ proguanil. In reports A and C, sleep deprivation and stress were mentioned as a possible influencing factor. Most travellers experience sleep deprivation, stress, jet lag, circadian rhythm disruptions, dietary changes, alcohol consumption, or illicit drug use while traveling, which can contribute to a psychotic disorder [19].

In cases A and B, the psychotic symptoms started within 2 days. In case C, the psychotic symptoms started after 12 days and in case D the latency time is unknown. Because malaria incubation period is about 8 to 25 days [20], and none

of the reported cases report fever or other malaria related symptoms, it is unlikely that malaria infection induced the psychotic symptoms.

The lifetime prevalence for any psychotic disorder is 3% [21] Psychotic disorder with the use of atovaquone/ proguanil is not widely described in literature. Halima Nakato *et al* [11] found neuropsychiatric ADRs with the use of atovaquone/ proguanil, however this difference was not significant compared to mefloquine. The US SmPC of the FDA mentions that psychotic events have been identified during postmarketing use of atovaquone/ proguanil [10].

Lareb received four reports of psychotic disorder with the use of atovaquone/ proguanil. Although the definition for psychotic disorder is broad and there is a high background incidence, literature is available which describes the occurrence of neuropsychiatric disorder with the use of atovaquone/ proguanil. This association is further strengthened by the disproportional RORs in the Lareb database, Eudravigilance database and WHO database. Because atovaquone/ proguanil is an alternative drug therapy especially when mefloquine is contraindicated in patients with a recent history psychiatric disorders [1], it is important to further investigate if atovaquone/ proguanil can also cause psychotic disorder.

- Further investigation of the information of the marketing authorization holders and other national centers is needed to evaluate the signal

*This signal has been raised on October 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB [www.cbqmeb.nl/cbq/en/default.htm](http://www.cbqmeb.nl/cbq/en/default.htm)*