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TRANSPARENCY COMMITTEE

OPINION

19 March 2008

SAVARINE, film-coated tablets
Pack of 14 (CIP: 341 278-9)
Pack of 28 (CIP: 341 279-5)

Applicant: ASTRAZENECA

Proguanil/chloroquine

ATC Code: P01BB51

List II

Marketing authorisation date: 08/07/1996

Reason for request:

The Committee has been asked by the Minister for Health and Solidarity to consider whether it would be appropriate:

1) for malaria chemoprophylaxis to be reimbursed by National Insurance for individuals living in areas of Guyana where malaria is not present and who travel to zones where malaria is endemic on a single occasion or infrequently, spending less than three months there.

2) for malaria chemoprophylaxis to be reimbursed by National Insurance for individuals living in Mayotte.

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

proguanil …….200 mg
chloroquine …… 100 mg

1.2. Indications

“This medicinal product is indicated in the prophylaxis of malaria for subjects travelling to endemic areas where the combination of chloroquine and proguanil is recommended.”

1.3. Dosage and method of administration

This medicinal product is a combination allowing daily dosing of chloroquine and proguanil in a single tablet.

Oral route

- Reserved for malaria prophylaxis in adults and adolescents aged from fifteen years and weighing at least 50 kg.

  Treatment should be instituted at least 24 hours before departure and continued throughout exposure to risk and for four weeks after leaving the area.

  The dosage is 1 tablet to be taken at the same time each day preferably with water and at the end of a meal.

  In order to prevent the occurrence of possible treatment-related sleep disorders, the tablet should be taken after the morning or midday meal.

- Elderly patients: It is not necessary to plan an adjustment in the dosage.
- Renal impairment and dialysed subjects: this medicinal product is contra-indicated in dialysed patients or subjects with renal impairment with a creatinine clearance below 60 ml/min. This medicinal product does not allow dosage adjustment in these subjects.
- Hepatic impairment: This medicinal product must be used with precaution in the case of hepatic insufficiency.

2 TRANSPARENCY COMMITTEE CONCLUSIONS

2.1. Actual benefit

2.1.1. Seriousness of the disease

Malaria is a serious illness, because it can be life-threatening if caused by Plasmodium falciparum. This parasitosis forms the subject of a WHO programme 1.
Chemoprophylaxis is mainly used in the case of risk of infection by Plasmodium falciparum, the outcome of which can be life-threatening. Moreover, this species is frequently resistant to some antimalarial drugs.

2.1.2. Efficacy/safety ratio

The fixed-dose proguanil-chloroquine combination is effective for the prevention of *P. falciparum* malaria. *P. falciparum* is frequently resistant to chloroquine and antifolinics (pyrimethamine and cycloguanil, the active metabolite of proguanil)[2].
This medicinal product is generally well tolerated (gastrointestinal disorders sometimes occur and, rarely, oral ulcerations caused by proguanil). Because of the presence of chloroquine, the proguanil-chloroquine combination is contra-indicated in subjects with retinopathy.

2.1.3. Therapeutic use

The Committee based its assessment on the recommendations of the French Public Health Council[3] which drafts health advice documents for travellers each year including an guide to the choice of antimalarial chemoprophylaxis according to region visited. The choice of antimalarial depends on:

- Place of stay,
- Pharmacokinetics, safety and efficacy of antimalarial agents on resistant strains,
- The traveller's age,
- Length of stay in the malarious area,
- Individual contraindications, in particular in subjects who must take other medication and in pregnant women.

Schedule 1 indicates the risk of malaria and the recommended chemoprophylaxis according to the areas visited (classified by WHO as group 1, 2 and 3, according to the frequency of resistance to chloroquine and proguanil).

The proguanil-chloroquine fixed-dose combination (SAVARINE) is one of the drugs of choice for the prevention of malaria in travellers visiting zones with a rare or moderate prevalence of chloroquine-resistance (group 2). The dosage strength of active ingredients in this medicinal product is not suitable for children under 15 years or adults or adolescents weighing under 50 Kg.

The actual benefit of this proprietary drug is substantial.

[1] World Health Organization. Guidelines for the treatment of malaria.
[2] CNR Malaria Management report 2006
[3] Recommendations published each year in the Weekly Epidemiological bulletin (BEH) of the National Sanitary Surveillance Institute (www.invs.sante.fr), under the aegis of the French Higher Public Health Council which has become the French Public Health Council (HCSP) – Health Recommendations for travellers - meeting of 12 June 2007.

2.2. Transparency Committee recommendations

As French Guiana and Mayotte are classified among the countries in group 3 [area of high prevalence of chloroquine-resistant and multiresistant *P. falciparum* (resistance to proguanil-cycloguanil and pyrimethamine)], the only antimalarial drugs usable for prophylaxis are mefloquine, atovaquone-proguanil and doxycycline. However, these treatments are not suitable for small children. Atovaquone-proguanil is indicated for chemoprophylaxis in children weighing 11 kg and over; and mefloquine for children weighing 15 kg and over, while doxycycline is contraindicated for children under 8 years old, and for pregnant and breast-feeding women.

In very rare cases, chloroquine + proguanil may represent an alternative to the recommended first-line antimalarial drugs (mefloquine, doxycycline, and atovaquone-proguanil) in the event of contraindications, poor tolerance or unsuitable dosage (especially in the case of children under 2-3 years old).

Offering chemoprophylaxis in an endemic malaria area is only feasible for people who do not live there on a long-term basis (and are therefore not immune), but will be staying temporarily in the area. This chemoprophylaxis recommendation is therefore justified in French Guiana for inhabitants of the coastal strip who visit the interior of the region, especially along the rivers on the border.
For inhabitants of Mayotte (endemic throughout the area), chemoprophylaxis is only justified for pregnant women, using intermittent preventive and curative treatment, preferably with sulphadoxine-pyrimethamine (FANSIDAR), the only currently approved treatment[4], using mefloquine prophylaxis [5,6], or using combined atovaquone-proguanil if mefloquine cannot be prescribed[7]. However, it is essential to provide insecticide-impregnated mosquito nets for the whole population, and take more effective measures against mosquito breeding areas.

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance to residents of French Guyana who do not live in malarial areas, but pay a single visit or occasional visits of under 3 months to areas where malaria is endemic.

The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Insurance to residents of Mayotte.

2.2.1. Packaging: Appropriate for the prescription conditions
2.2.2. Reimbursement rate: 65%

[4] World Health Organization: Lives at risk: malaria in pregnancy. In: *http://www.who.int/features/2003/04b/fr/*

[5] Steketee RW, Wirima JJ, Slutsker L et al. Malaria parasite infection during pregnancy and at delivery in mother, placenta and new born: efficacy of chloroquine and mefloquine in rural Malawi. Am J Trop Med Hyg 1996; 55: 24-32.

[6] Menendes C et al. Reducing the burden of malaria in pregnancy by preventive strategies. The Lancet Infect Dis 2007: 126-135

[7] However, monitoring of pregnancies exposed to the atovaquone-proguanil combination is insufficient to rule out all risks. Consequently, the use of MALARONE in pregnant woman could be considered if necessary (see SPC).

Schedule 1

Malaria risk, and prophylaxis recommended for each country (extract from BEH 24/12 June 2007).

Table 1: List of countries requiring antimalarial prophylaxis, 2007		
Country [1]	**Malaria situation 2007/ prophylaxis [2]**	**For a visit of under 7 days: prophylaxis optional [3]**
Afghanistan	group 3	for the whole country
South Africa	North-east: group 3; elsewhere: no prophylaxis	
Angola	group 3	
Saudi Arabia	South-west: group 3; elsewhere: no prophylaxis	for the whole country
Argentina (*)	North: group 1; elsewhere: no prophylaxis	for the whole country
Bangladesh	Dacca: no prophylaxis rest of country: group 3	
Belize (*)	group 1	for the whole country
Benin	group 3	
Bhutan	group 3	for the whole country
Bolivia	Amazonia: group 3; elsewhere (*): group 1	for the whole country except Amazonia
Botswana	group 3	
Brazil	Amazonia: group 3; elsewhere: group 2	
Burkina Faso	group 2	
Burundi	group 3	
Cambodia	group 3	
Cameroon	group 3	
China	Yunnan and Hainan: group 3; North-east (*): group 1	whole country except Yunnan and Hainan
Colombia	Amazonia: group 3; elsewhere: group 2	
Comores	group 3	
Congo	group 3	
Costa Rica (*)	group 1	for the whole country
Ivory Coast	group 3	
Djibouti	group 3	
Ecuador	Amazonia: group 3; elsewhere: group 1	
Eritrea	group 3	
Ethiopia	group 3	
Gabon	group 3	
Gambia	group 3	
Ghana	group 3	
Guatemala (*)	group 1	for the whole country
Guinea	group 3	
Guinea-Bissau	group 3	
Equatorial Guinea	group 3	
Guyana	group 3	
French Guiana	Rivers: group 3; coastal areas: no prophylaxis	
Haiti	group 1	
Honduras (*)	group 1	for the whole country
India	State of Assam: group 3; elsewhere; group 2	
Indonesia	Bali: no prophylaxis; elsewhere: group 3	
Iran	South-east: group 3; elsewhere (*): group 1	for the whole country
Iraq (*)	group 1	for the whole country
Jamaica	group 1: Kingston only	

Kenya	group 3	
Laos	group 3	
Liberia	group 3	
Madagascar	group 2	
Malaysia	urban or coastal areas: no prophylaxis; elsewhere: group 3	
Malawi	group 3	
Mali	group 2	
Mauritania	group 2	
Mayotte (departmental community)	group 3	for the whole country
Mexico (*)	group 1	for the whole country
Mozambique	group 3	
Myanmar (formerly Burma)	group 3	
Namibia	group 3	
Nepal	Terai: group 2; elsewhere: no prophylaxis	
Nicaragua (*)	group 1	for the whole country
Niger	group 2	
Nigeria	group 3	
Uganda	group 3	
Pakistan	group 3	
Panama (*)	West: group 1; East: group 3	West Panama
Papua New Guinea	group 3	
Paraguay	East (*): group 1; elsewhere: no prophylaxis	for the whole country
Peru	Amazonia: group 3; elsewhere (*): group 1	for the whole country except Amazonia
Philippines	group 3	
Dominican Republic	group 1	
Central African Republic	group 3	
Democratic Republic of Congo (formerly Zaire)	group 3	
Rwanda	group 3	
El Salvador (*)	group 1	for the whole country
São Tomé and Principe	group 3	
Solomon Islands	group 3	
Senegal	group 3	
Sierra Leone	group 3	
Somalia	group 3	
Sudan	group 3	
Sri Lanka (*)	group 2	for the whole country
Surinam	group 3	
Swaziland	group 3	
Tajikistan (*)	group 2	for the whole country
Tanzania	group 3	
Chad	group 2	
Thailand	Border areas with Cambodia, Laos, Myanmar and Malaysia: group 3; elsewhere: no prophylaxis	for the whole country except the borders with Cambodia, Laos, Myanmar and Malaysia
Timor East	group 3	
Togo	group 3	
Vanuatu	group 2	
Venezuela (Amazonia)	Amazonia: group 3; elsewhere (*): group 1	
Vietnam	Coastal strip and deltas: no prophylaxis; elsewhere: group 3	for the coastal strip and deltas
Yemen	group 3	
Zambia	group 3	
Zimbabwe	group 3	

(*) Mainly *Plasmodium vivax.*

(1) In the case of Africa, good knowledge of the areas of resistance visited by French travellers has enabled a zone 2 and a zone 3 to be identified. This distinction does not appear in the WHO or CDC recommendations.

(2) Group 1: chloroquine; group 2: chloroquine+proguanil or atovaquone+proguanil; group 3: mefloquine or atovaquone+proguanil or doxycycline.

(3) In these regions, chemoprophylaxis is not essential for a stay of less than 7 days, provided that the traveller is in a position to consult a doctor urgently in the event of fever during the months after returning home.

2.2.3. Chemoprophylaxis according to area

COUNTRIES IN GROUP 0: non-malarial areas: no prophylaxis

Africa: Egypt, Lesotho, Libya, Réunion, Saint Helena, Seychelles, Tunisia.

America: all towns (except in Amazonia) and Antigua and Barbuda, Netherlands Antilles, Bahamas, Barbados, Bermuda Islands, Canada, Chile, Cuba, Dominica, United States, Guadeloupe, Grenada, Cayman Islands, Falkland Islands, Virgin Islands, Martinique, Puerto Rico, Santa Lucia, Trinidad and Tobago, Uruguay.

Asia: all towns (except in India) and Brunei, Guam, Hong Kong, Japan, Kazakhstan, Macao, Maldives, Mongolia, Singapore, Taiwan.

Europe: all countries (including the Azores, Canaries, Cyprus, Russian Federation, Baltic States, Ukraine, Belarus and European Turkey).

Near and Middle East: all towns and Bahrain, United Arab Emirates, Israel, Jordan, Kuwait, Lebanon, Qatar.

Australasia: all towns and Australia, Fiji, Hawaii, Mariana Islands, Marshall Islands, Micronesia, New Caledonia, New Zealand, Easter Island, French Polynesia, Samoa, Tonga, Tuvalu, Wallis and Futuna, Kiribati, Cook, Western Samoa, Niue, Nauru, Palau.

COUNTRIES IN GROUPS 1, 2 and 3 (see Tables 1 and 2)
GROUP 1: areas without chloroquine resistance:
- Chloroquine (Nivaquine® 100)

GROUP 2: areas of chloroquine resistance
- Chloroquine (Nivaquine® 100) and proguanil (Paludrine® 100)
- Combined chloroquine-proguanil (Savarine®)
- Combined atovaquone-proguanil (Malarone®)

GROUP 3: areas of high prevalence of chloroquine resistance and multiresistance:
- Mefloquine (Lariam® 250)
- Combined atovaquone-proguanil (Malarone®)
- Doxycycline monohydrate.

It is not advisable for pregnant women to visit the countries in this group. Note that there are some areas of mefloquine resistance: East Timor, forest areas of Thailand, and border areas of Cambodia, Myanmar (formerly Burma) and Laos.

SPECIAL CASES

Short stays in low-risk areas: for a short stay (under 7 days: the minimum incubation period of malaria caused by *P. falciparu*m) in areas with a low risk of transmission, prophylaxis is not essential, provided that the rules of protection against mosquitoes are strictly followed and that the traveller is in a position to consult a doctor urgently in the event of fever during the months after returning home and informs the doctor that an endemic malaria area has been visited. These regions are indicated in the third column of Table 1.

Sporadic transmission areas: prophylaxis is not essential in the countries listed below, whatever the duration of the stay; however, the traveller must be in a position to consult a doctor urgently in case of fever during the stay and during the next few months after returning home.

Africa: Algeria, Cape Verde, Morocco, Mauritius.

Asia: Armenia, Azerbaijan, South Korea, North Korea, South-east Georgia, Kyrgyzstan, Uzbekistan, Turkmenistan.

Near and Middle East: Oman, Syria, South-east Turkey.

Variability of transmission levels according to regions of countries
The division of areas of resistance by *Plasmodium falciparum* as indicated in Table 1 should be adjusted on the basis of transmission levels. Identifying the country of destination is insufficient; account must also be taken of the region visited, the conditions of the stay, and the season. For example, a visit to Thailand or Vietnam not involving an overnight stay in forest areas does not normally require antimalarial prevention. Conversely, malaria is once again endemic in some towns in India and Amazonia.
Malaria is not usually transmitted above an altitude of 1500 metres in Africa and 2500 metres in America and Asia.

2.2.4. Long stays (over three months)

Detailed information should be given about malarial prevention. It is useful to deliver a document drawn up according to destination. It is also essential to ensure that the information given is thoroughly understood. The need for protection against mosquito bites (mosquito netting, etc.) should also be emphasized. During the first visit, it is essential for prophylaxis adapted to the level of resistance to be continued for at least the first six months, except in the case of combined atovaquone-proguanil, for which insufficient information about long-term use is available. Beyond that date, as it seems unrealistic for prophylaxis to continue for several years, it can be adjusted on the advice of local doctors. Intermittent prophylaxis during the rainy season or certain journeys may be the best solution. In all cases, a doctor should be consulted rapidly in the event of fever.
Travellers should be warned that the risk of a serious attack persists for two months after their return from the endemic area.

2.3. Symptomatic treatment

Antimalarial treatment without medical advice during the stay should be the exception rather than the rule, and is only appropriate **if medical advice cannot be obtained within 12 hours**. It should always be based on a prescription issued by a doctor before exposure.

<table>
<tr><th colspan="4">Table 2: Antimalarial prophylaxis by resistance patterns, 2007</th></tr>
<tr><th>Chemo-resistance group</th><th>Adult</th><th>Pregnant woman</th><th>child</th></tr>
<tr><td>Group 1</td><td colspan="2">CHLOROQUINE
(Nivaquine®)
100 mg/day
Stay + 4 weeks after</td><td>CHLOROQUINE
(Nivaquine®)
1.5 mg/kg/day
Stay + 4 weeks after</td></tr>
<tr><td rowspan="2">Group 2</td><td colspan="2">CHLOROQUINE + PROGUANIL
100 mg/day 200 mg/day
(Nivaquine® + Paludrine®) or (Savarine®)
Stay + 4 weeks after</td><td>CHLOROQUINE + PROGUANIL
1.5 mg/kg/day 3 mg/kg/day
(Nivaquine®) (Paludrine®)
Stay + 4 weeks after</td></tr>
<tr><td rowspan="3">Group 3</td><td>ATOVAQUONE 250 mg
+
PROGUANIL 100 mg
(Malarone®) 1 tab/day
Stay + 1 week after</td><td>ATOVAQUONE 250 mg
+
PROGUANIL 100 mg
May be considered if necessary</td><td>- If < 11 kg. as above
- If ≥ 11 kg and < 40 kg:
ATOVAQUONE 62.5 mg
+ PROGUANIL 25 mg
(Malarone paediatric®) 1 tab/10 kg/day
Stay + 1 week after</td></tr>
<tr><td colspan="2">MEFLOQUINE 250 mg /(Lariam®)
1 tab/week
10 days before + stay + 3 weeks after</td><td>If > 15 kg: MEFLOQUINE
(Lariam®)
5 mg/kg/week
10 days before + stay + 3 weeks after</td></tr>
<tr><td>DOXYCYCLINE
(doxycycline monohydrate)
100 mg/day
stay + 4 weeks after</td><td>-</td><td>If > 8 years: DOXYCYCLINE
(doxycycline monohydrate)
50 mg/day if < 40 kg
stay + 4 weeks after</td></tr>
</table>