Malaria Background Information

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Abstract

Figure 1

WHAT IS MALARIA?

Malaria is a serious and often fatal disease caused by the malarial parasite. There are four species of malarial parasite: Plasmodium (P) falciparum, P. vivax, P. ovale and P. malariae. Of these, P. falciparum is the most life threatening, accounting for the majority of malaria deaths in the developing world[1].

The malaria disease cycle is dependent on transmission between people by mosquitoes (see “How Malaria Spreads” diagram in editor's note) [2]. A single bite from an infected mosquito can lead to malaria[2]. Following the bite, the parasite travels to the liver within 30 minutes and starts to reproduce rapidly. This process can take between five and 16 days, however some parasites lie dormant in the liver and may only become active years later.

The parasites travel from the liver to the bloodstream, enter the red blood cells and continue to reproduce. The red blood cells eventually rupture, releasing more parasites into the bloodstream to infect other red blood cells. This repeating cycle depletes the body of oxygen and coincides with the onset of fever and chills. It is both the direct action of the parasite and the body's response to the parasitic infection that lead to the symptoms of malaria[1].

EPIDEMIOLOGY OF MALARIA

Symptoms of malaria may include fever, shivering, headache, repeated vomiting, diarrhoea, generalised convulsions, pain in the joints and backache[1].

Approximately 40 percent of the world's population – mostly those living in the poorest countries – are at risk for malaria[1]. High malaria risk areas include large portions of Central and South America, Africa, the Indian subcontinent, Southeast Asia and the Middle East[3].

Worldwide, the World Health Organisation (WHO) has estimated that there are 300 million malaria cases annually, directly causing over one million deaths[1]. Malaria kills one child every 30 seconds, while many children who survive an episode of severe malaria suffer from learning impairments or brain damage[1].

MALARIA IN AFRICA

More than 90 percent of malaria cases and the great majority of deaths occur in tropical Africa where P.falciparum malaria is the most common[4]. Malaria represents 10 percent of the continent's overall disease burden[5]. Hundreds of millions of African children and adults are chronically infected with malaria. Between 30 and 50 percent of inpatient admissions and 50 percent of outpatient visits are attributed to malaria each year[5].

Economists estimate that acute and chronic malarial infection substantially reduces the Gross Domestic Product (GDP) growth in countries with high malaria transmission rates compared to countries with lower malaria infection rates[5].

GSK'S COMMITMENT IN THE FIGHT AGAINST MALARIA

GSK has a dedicated group based in the UK, US and Spain which has been created within GSK's pharmaceutical R&D organisation to ensure a focus on diseases of the developing world. Projects are prioritised primarily on their socio-economic and public health benefits rather than their commercial returns. Some of these projects are carried out in collaboration with, and funding from, the WHO and Medicines for Malaria Venture (MMV).

Since 1999, GSK has also been part of a public-private

partnerships including the WHO/TDR (Tropical Disease Research Programme of the World Health Organization), the UK Department for International Development (DFID), the University of Liverpool, the Liverpool School of Tropical Medicine, the London School of Hygiene and Tropical Medicine, and African researchers, with initial support by an early grant from the Wellcome Trust, to develop effective, affordable antimalarials for sub-Saharan Africa. The partnership has successfully developed LAPDAP™ (chlorproguanil/dapsone), a synergistic combination which is a valuable addition to the armamentarium of antimalarial drugs used in sub-Saharan Africa.

MALARIA PIPELINE

CDA, an artemisinin-based combination of chlorproguanil-dapsone-artesunate, is moving into Phase III clinical development in November 2005. In Phase II trials, this compound produced a rapid therapeutic response and is active against the multi-drug resistant P.falciparum malaria. CDA is being developed by GSK in partnership with the WHO/TDR, MMV, the University of Liverpool, Liverpool School of Tropical Medicine and the London School of Hygiene and Tropical Medicine.

Isoquine is an antimalarial compound in early development in partnership between GSK, the MMV and University of Liverpool. At this stage, the molecule has good activity in drug-resistant parasites, with no cross-resistance. The plan is to begin human studies in 2006 and investigate the opportunities available for combination therapy.

Pyridones are a novel class of antimalarial agents being investigated by GSK and the MMV. Pyridones work by inhibiting the energy processes of the microorganism that causes malaria. In 2004, GSK and the MMV identified GW844520 as the first drug candidate to emerge from one of four projects in the GSK-MMV ‘mini-portfolio' research collaboration.

Vaccines are another important area for malaria control. GSK Biologicals is developing the world's most advanced malaria vaccine candidate, which was shown to be 58 percent effective in preventing severe disease in one-to-four year-olds in a groundbreaking proof-of-concept study conducted in Mozambique in 2004. In partnership with PATH's Malaria Vaccine Initiative, GSK is moving the vaccine candidate RTS,S into advanced clinical trials in several African countries. GSK recognizes the importance of improved health for everyone in the developing world and is the only major pharmaceutical company that is developing vaccine for malaria, tuberculosis and HIV.

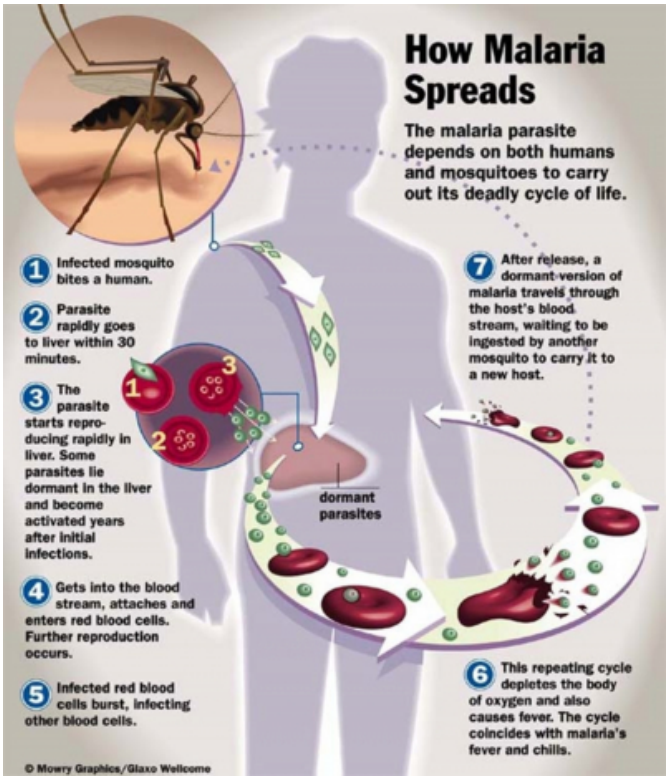
GSK'S KEY MARKETED PRODUCTS AND DEVELOPMENT PIPELINE FOR DISEASES OF THE DEVELOPING WORLD

Figure 2

DISEASE	PRE-CLINICAL ACTIVITY	PHASE I	PHASE II	PHASE III	MARKETED PRODUCTS
Malaria	✓			Tafenoquine (prophylaxis) CDA (chlorproguanil + dapsone + artesunate)	Lapdap Halfan Malarone
HIV	✓		Protease Inhibitor (brecanavir)		Retrovir Epivir Combivir Ziagen Trizivir Agenerase Epzicom/Kivexa Lexiva/Telzir
Vaccines	✓	HIV TB	**N.meningitides** RTS,S (malaria) Hepatitis E Dengue fever	Streptorix (*S.pneumoniae* paediatric) Cervarix (cervical cancer)	Rotarix (Rotavirus) Havrix (Hepatitis A) Energix-B (Hepatitis B) Infanrix (Diptheria, tetanus, wholecell Pertussis) Polio Sabin (Polio) Priorix (Measles, mumps and rubella) Typherix (Typhoid) Hiberix (*Haemophilus influenzae* type b) Mencevax ACW (Meningitis)
Tuberculosis	✓				
Other	✓			Sitamaquine (visceral leishmaniasis)	Zentel (De-worming agent) Pentostam (Visceral leishmaniasis) Banocide (Lymphatic Filariasis – GSK India)

EDITOR'S NOTE

Figure 3



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