ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mosquirix powder and suspension for suspension for injection

Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 mL) contains 25 micrograms of RTS,S[1,2] adjuvanted with $AS01_E$[3].

[1] Portion of *P. falciparum* circumsporozoite protein fused with hepatitis B surface antigen (RTS), and combined with hepatitis B surface antigen (S)

[2] in the form of non-infectious virus-like particles (VLPs) produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

[3] $AS01_E$ adjuvant is composed of *Quillaja saponaria* Molina, fraction 21 (QS-21) (25 micrograms) and 3-O-desacyl-4'- monophosphoryl lipid A (MPL) (25 micrograms)

Excipient with known effect

This vaccine contains 0.03 mg of polysorbate 80 per dose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.

The powder is white.
The suspension is an opalescent, colourless to pale brownish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mosquirix is indicated for active immunisation of children aged 6 weeks up to 17 months (at the time of the first dose) against malaria caused by *Plasmodium falciparum* and against hepatitis B (see sections 4.2, 4.4 and 5.1).

The use of Mosquirix should be based on official recommendations considering *Plasmodium falciparum* malaria epidemiology in different geographical areas.

4.2 Posology and method of administration

Posology

Vaccination in children from 6 weeks up to 17 months of age (at first dose):

- Three doses, each of 0.5 mL, should be given at monthly intervals.
- A fourth dose is recommended from 12 to 18 months after the third dose.
- After the fourth dose, annual revaccination until 5 years of age may be considered (see section 5.1).

The safety and efficacy of Mosquirix in children younger than 6 weeks and older than 17 months of age (at first dose) have not been established.

Method of administration

Mosquirix is for intramuscular injection only.

The anterolateral thigh is the preferred site for injection in children younger than 5 months of age. The deltoid muscle is the preferred site for injection in children aged 5 months and older (see sections 4.4 and 4.5).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Hypersensitivity to a previous dose of Mosquirix or hepatitis B vaccines.

4.4 Special warnings and precautions for use

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable effects) and a clinical examination.

As with other vaccines, vaccination with Mosquirix should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

A history of febrile convulsions or a family history of convulsions does not constitute a contraindication for the use of Mosquirix. Vaccinees, especially those with a history of febrile convulsions, should be closely followed up as vaccine related fever may occur after vaccination (see section 4.8). In case of fever, antipyretic measures should be initiated according to local guidelines.

Fever may follow each dose of Mosquirix (see section 4.8). Clinical data generated with other paediatric vaccines suggest that the prophylactic use of paracetamol might reduce the immune response to vaccine antigens. The clinical relevance of this observation remains unknown. In absence of clinical data with Mosquirix, the routine use of prophylactic antipyretic medicinal products before vaccination is therefore not recommended.

Protection against P. falciparum malaria

Mosquirix does not provide complete protection against malaria caused by *P. falciparum* (see section 5.1).

Protection against *P. falciparum* malaria wanes over time and vaccination may delay the acquisition of natural immunity (see section 5.1). If symptoms compatible with malaria develop, appropriate diagnosis and treatment should be sought.

Data regarding the efficacy of Mosquirix are limited to children from sub-Saharan Africa.

Mosquirix will not protect against malaria caused by pathogens other than *Plasmodium falciparum*.

The use of other malaria control measures recommended locally should not be interrupted.

Protection against hepatitis B

Mosquirix should not be used for the prevention of hepatitis B in settings where prevention against malaria caused by *P. falciparum* is not sought. An immune response against hepatitis B may not be elicited in all vaccinees (see section 5.1).
Mosquirix will not protect against hepatitis caused by other pathogens other than hepatitis B virus.

Meningitis

In clinical studies, meningitis (any aetiology) has been reported more frequently in the group vaccinated with three doses of Mosquirix up to 20 months post dose 1 (27 cases out of 11,439 vaccinees) compared with the control group (4 cases out of 6,096 vaccinees). A causal relationship to the vaccine has not been established.

Systemic immunosuppressive medications and immunodeficiency

There are no data in children receiving immunosuppressive treatment or children with immunodeficiencies other than HIV infection. In these children, it cannot be ruled out that efficacy is impaired. Limited data are available with HIV-infected children (see sections 4.8 and 5.1).

Precautions for use

Do not administer the vaccine intravascularly, intradermally or subcutaneously.

Patients at risk of bleeding

As with other vaccines administered intramuscularly, Mosquirix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Preterm infants

The potential risk of apnoea and the need for respiratory monitoring for 48 to 72 h should be considered when administering the first three doses to very preterm infants (born ≤ 28 weeks of gestation) who remain hospitalised at the time of vaccination and particularly for those with a previous history of respiratory immaturity.

Excipients

This vaccine contains 0.03 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions.

This vaccine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially ‘potassium-free’.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

Use with other vaccines

If Mosquirix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Mosquirix can be given concomitantly with any of the following monovalent or combination vaccines including diphtheria (D), tetanus (T), whole cell pertussis (Pw), acellular pertussis (Pa), hepatitis B (HepB),

Haemophilus influenzae type b (Hib), oral polio (OPV), measles, rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines (PCV). The co-administration of Mosquirix with PCV increases the risk of fever within 7 days post-vaccination (see section 4.8).

Concomitant administration of rotavirus and pneumococcal conjugate vaccines with Mosquirix may reduce the antibody response to the circumsporozoite (CS) antigen of Mosquirix. The impact of this observation on the level of protection induced by Mosquirix is currently unknown.

Use with chemoprevention

Mosquirix can be given in combination with Seasonal Malaria Chemoprevention (SMC) (see section 5.1).

Use with systemic immunosuppressive medications

In the absence of data it cannot be ruled out that efficacy is impaired in children receiving immunosuppressive treatment.

Use with prophylactic administration of antipyretics

See section 4.4.

4.6 Fertility, pregnancy and lactation

There are no or limited amount of data from the use of Mosquirix in pregnant women. No animal studies were performed with Mosquirix with respect to reproductive toxicity.

Mosquirix is not intended for use in women of childbearing potential.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies, the most serious adverse reaction associated with Mosquirix was febrile seizures (within 7 days post-vaccination) (0.1%). The most commonly reported adverse reactions were fever (27%), irritability (14%) and injection site reactions such as pain (16%) and swelling (7%).

Tabulated list of adverse reactions

The safety profile presented below is based on a pooled analysis of more than 11 000 children who have been vaccinated in clinical studies with three doses of Mosquirix (Table 1).

In children who received additional doses (up to a total of six doses), there was no increase in frequency of adverse reactions, except for decreased appetite which was reported very commonly after only the fourth dose. All other adverse reactions occurred at the same or lower frequency as reported in Table 1.

Adverse reactions reported are listed according to the following frequency:

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)

Table 1: Adverse reactions reported after three doses of the vaccine

System Organ Class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Common	decreased appetite
Psychiatric disorders	Very common	irritability
Nervous system disorders	Common	somnolence
	Uncommon	febrile convulsions (within 7 days post-vaccination)
Gastrointestinal disorders	Common	diarrhoea
	Uncommon	vomiting
General disorders and administration site conditions	Very common	fever, injection site reactions (including swelling, erythema and pain)
	Uncommon	injection site induration

Other special populations

HIV-infected children

Data from clinical studies suggest that HIV-infected children are more likely to experience local and systemic reactogenicity (injection site pain and injection site erythema, fever, somnolence, irritability, decreased appetite) compared to children of unknown HIV infection status.

Description of selected adverse reactions

Fever

In a clinical study in infants aged 8-12 weeks, fever was reported more frequently in infants receiving PCV in co-administration with Mosquirix, DTPa/Hib and OPV simultaneously (26%), as compared to infants receiving only Mosquirix, DTPa/Hib and OPV (14%). The frequency of grade 3 fever on co-administration (defined as axillary temperature > 39.0 °C) was ≤ 1%.

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.

4.9 Overdose

No case of overdose has been reported. In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, malaria vaccines, ATC code: J07XA01

Mechanism of action

Mosquirix is a pre-erythrocytic vaccine intended to limit the ability of *Plasmodium falciparum* to infect, mature and multiply in the liver by eliciting humoral and cellular immunity to the circumsporozoite (CS) protein, which is abundantly present at the surface of the sporozoite.

Mosquirix induces antibodies against hepatitis B surface antigen (anti-HBs antibodies).

Vaccine efficacy

Pivotal Phase III study (Malaria-055)

In a Phase III randomised controlled double-blind study conducted at 11 centres in 7 sub-Saharan African countries with a wide range of transmission intensities, more than 15 000 children from two age groups (6-12 weeks and 5-17 months) were enrolled to evaluate efficacy and safety of Mosquirix when given according to a 0, 1, 2-month schedule. In addition, more than 4 200 children (including children from both age groups) received a fourth dose, given 18 months after the third dose.

Children from the 6-12 weeks age group received Mosquirix concomitantly with DTPw-HepB+Hib and OPV vaccines.

The primary objective of the study was efficacy against first or only episode of clinical malaria over a follow-up period of 12 months after three doses in each age group.

The secondary objectives included efficacy against all episodes of clinical malaria, efficacy against severe malaria and efficacy against hospitalisation caused by malaria over different follow-up periods after three doses in each age group.

The efficacy of Mosquirix was evaluated in the context of high insecticide treated bed nets coverage (86% in the 6-12 weeks age group and 78% in the 5-17 months age group).

Infants aged 6-12 weeks (at first dose)

In infants aged 6-12 weeks, the vaccine efficacy (VE) against first or only episode of clinical malaria over 12 months of follow-up (co-primary objective) was 31% (97.5% CI: 24; 38).

A summary of the secondary objectives pertaining to VE over different follow-up periods, in infants who received three doses only or three doses plus a fourth dose, is given in Table 2.

Table 2: Malaria-055: vaccine efficacy in infants aged 6-12 weeks at first dose

	Vaccine efficacy against all episodes of clinical malaria (95% CI)	**Vaccine efficacy against severe malaria** (95% CI)	**Vaccine efficacy against hospitalisation caused by malaria** (95% CI)
Over 12 months follow-up from dose 3 (ATP* cohort, N = 6003)	33% (26; 39)	37% (5; 58)	32% (7; 50)
Over 18 months follow-up from dose 3 (ATP* cohort, N=6003)	27% (20; 32)	15% (-20; 39)	17% (-7; 36)
3 doses only (ATP* cohort, N=5 997)			
Over 30 months follow-up from dose 3	20% (13; 27)	11% (-22; 35)	10% (-15; 30)
Over 36 months follow-up from dose 3**	18% (11; 25)	13% (-17; 35)	13% (-9; 31)
3 doses + 4th dose (ATP* cohort, N=5 997)			
Over 30 months follow-up from dose 3	28% (22; 34)	17% (-14; 40)	25% (3; 42)
Over 36 months follow-up from dose 3**	27% (21; 32)	21% (-7; 42)	27% (7; 43)

*According-to-protocol (ATP) cohort: all infants immunised according to schedule, N= total number in all 3 study groups

** The follow-up period from dose 3 to study end was not the same for all subjects because the study ended on a fixed date. The median length for this follow-up period is 36 months.

Children aged 5-17 months (at first dose)

In children aged 5-17 months, the VE against first or only episode of clinical malaria over 12 months of follow-up (co-primary objective) was 56% (97.5% CI: 51; 60).

A summary of the secondary objectives pertaining to VE over different follow-up periods, in children who received three doses only or three doses plus a fourth dose, is given in Table 3.

Table 3: Malaria-055: vaccine efficacy in children aged 5-17 months at first dose

	Vaccine efficacy against clinical malaria (95% CI)	**Vaccine efficacy against severe malaria** (95% CI)	**Vaccine efficacy against hospitalisation caused by malaria** (95% CI)
Over 12 months follow-up from dose 3 (ATP* cohort, N=6880)	51% (47; 55)	45% (22; 60)	48% (35; 59)
Over 18 months follow-up from dose 3 (ATP* cohort, N=6885)	46% (42; 49)	36% (15; 51)	42% (29; 52)
3 doses only (ATP* cohort, N=6 918)			
Over 30 months follow-up from dose 3	34% (29; 39)	2% (-28; 25)	18% (1; 32)
Over 46 months follow-up from dose 3**	26% (21; 31)	-6% (-35; 17)	12% (-5; 26)
3 doses + 4th dose (ATP* cohort, N=6 918)			
Over 30 months follow-up from dose 3	46% (42; 50)	32% (10; 50)	40% (26; 52)
Over 46 months follow-up from dose 3**	39% (34; 43)	29% (6; 46)	37% (24; 49)

*According-to-protocol (ATP) cohort: all children immunised according to schedule, N= total number in all 3 study groups

** The follow-up period from dose 3 to study end was not the same for all subjects because the study ended on a fixed date. The median length for this follow-up period is 46 months.

Long-term follow-up of efficacy

The Phase III efficacy study was extended for 3 additional calendar years in 3 out of the 11 centres (follow-up study Malaria-076). Vaccine efficacy from the first vaccine dose given in the efficacy study to the end of the follow-up (median duration of follow-up: 6.2 years in infants aged 6-12 weeks at first dose and 6.8 years in children aged 5-17 months at first dose) is presented in Table 4.

Table 4: Malaria-055/-076: vaccine efficacy from first vaccine dose to the end of the follow-up

	Vaccine efficacy against clinical malaria (95% CI)	**Vaccine efficacy against severe malaria** (95% CI)
Infants aged 6-12 weeks at first dose (ITT cohort, N= 1 905)		
3 doses only	13% (4; 21)	34% (9; 53)
3 doses + 4th dose	16% (7; 24)	31% (5; 50)
In children aged 5-17 months at first dose (ITT cohort, N= 2 512).		
3 doses only	19% (11; 27)	10% (-18; 32)
3 doses + 4th dose	24% (16; 31)	37% (15; 53)

ITT= Intent-to-treat population
N= total number of subjects

Protective efficacy in other studies

Vaccine efficacy following vaccination with up to six doses (primary schedule and three yearly revaccinations of Mosquirix)

In a Phase IIb randomised, open-label, controlled, multi-centre study (Malaria-094) the VE was evaluated in children aged 5-17 months (at time of first dose) with a primary vaccination of three doses followed by either a fourth dose at 18 months after dose three or in a second group up to three yearly doses of vaccine. VE was similar when the fourth dose was given at 12 months or 18 months after the third dose [51% (95% CI: 35; 63) and 43% (95% CI: 21; 59), respectively]

Vaccine efficacy against all episodes of clinical malaria in the group receiving two additional yearly revaccinations after a fourth dose at 12 months is given in Table 5.

Over the whole period of 50 months the VE was 32% (95% CI: 14; 47) in the 0, 1, 2, 20-month schedule group, versus (vs) 48% (95% CI: 33; 59) in the group vaccinated according to a schedule of 0, 1, 2, 14, 26, 38-months.

Table 5: Malaria-094: vaccine efficacy against clinical malaria (all episodes) following a fourth, fifth and sixth annual dose in children aged 5-17 months (at first dose)

Study period	**Time period**	**N**	**Vaccine efficacy against clinical malaria (95% CI)**
Over 12 months follow-up from dose 4	Month 14-Month 26	245	51% (35; 63)
Over 12 months follow-up from dose 5	Month 26-Month 38	232	57% (39; 69)
Over 12 months follow-up from dose 6	Month 38-Month 50	221	34% (7; 54)

N = number of vaccinated subjects in the Per Protocol Set for Efficacy

Vaccine efficacy following Mosquirix vaccination with Seasonal Malaria Chemoprevention (SMC)

A Phase IIIb randomised, double-blind, placebo-controlled study (Malaria-099; 2-year extension Malaria-106), involving 5 920 children aged 5-17 months assessed the efficacy of seasonal vaccination of Mosquirix

with SMC compared to either Mosquirix or SMC alone over 5 years in areas with seasonal high malaria transmission. Mosquirix was given as a primary three dose schedule (at 1-month intervals) and subsequent yearly single doses with or without SMC, prior to the transmission season. SMC comprises the administration of anti-malarial drugs, such as sulfadoxine – pyrimethamine and amodiaquine, at monthly intervals, during the peak malaria transmission season each year.

Mosquirix was non-inferior to SMC (hazard ratio comparing Mosquirix with SMC over the 5-year period was 1,03 [95% CI: 0,95; 1,12]) in protecting against uncomplicated clinical malaria. Non-inferiority was demonstrated if the upper limit of the 95% CI for the hazard ratio between groups was lower than 1,2. Vaccination of Mosquirix with SMC (up to seven doses) provided superior vaccine efficacy as compared to Mosquirix or SMC alone. Superiority was defined as a 12% difference in the incidence of clinical malaria between the combined and single intervention groups.

The protective efficacy against clinical and severe malaria outcomes is presented in Table 6 for the first 3 years of the study (three primary doses and two additional yearly doses of Mosquirix) and for the 5 years study period (three primary doses and four additional yearly doses of Mosquirix).

Table 6: Malaria-099/-106: protective efficacy of the combination of Mosquirix and SMC vs. Mosquirix alone or SMC alone in children aged 5-17 months (at first dose)

	Protective efficacy of Mosquirix with SMC (95% CI)			
	***Vs.* Mosquirix alone**		***Vs.* SMC alone**	
	Over 3 years	**Over 5 years**	**Over 3 years**	**Over 5 years**
Clinical malaria*	60% (55; 64)	59% (55; 63)	63% (58; 67)	58% (53; 62)
Hospital admission with severe malaria	71% (42; 85)	66% (38; 81)	71% (42; 85)	67% (40; 82)

Modified intention-to-treat population (all eligible children whose parents or guardians provided consent and who received a first dose of trial vaccine or vaccine placebo)

*All episodes

Vaccine-induced immunogenicity

No correlate of protection has currently been established.

Immunogenicity against the circumsporozoite (CS) protein

In the Phase III efficacy study, the geometric mean concentration (GMC) of antibodies against the circumsporozoite (CS) protein, was measured after the third dose of Mosquirix (month 3) as well as before and after the fourth dose (months 20 and 21) in a subset within each age group.

Antibody responses for each age group are given in Table 7.

Table 7: Malaria-055: antibody responses to Mosquirix (anti-CS antibody)

	Anti-CS antibody GMC		
	One month after the third dose (month 3) (95% CI)	**Before the fourth dose (month 20)** (95% CI)	**One month after the fourth dose (month 21)** (95% CI)
Infants (aged 6-12 weeks at first dose)	N=1221	N=530	N=503
	211 EU/mL (198; 224)	6 EU/mL (5; 7)	170 EU/mL (154; 188)
Children (aged 5-17 months at first dose)	N=1034	N=442	N=426
	621 EU/mL (592; 652)	34 EU/mL (31; 39)	318 EU/mL (295; 343)

N= total number of children/infants immunised according to schedule (ATP cohort) with available results

Two studies evaluated the immunogenicity of Mosquirix. The geometric mean concentration (GMC) of antibodies against the circumsporozoite (CS) protein, from Malaria-094 and Malaria-099 after primary vaccination and after yearly revaccinations are shown in Table 8.

Table 8: Malaria-094 and Malaria-099: antibody responses to Mosquirix (anti-CS antibody) after annual revaccination

	Malaria-094		**Malaria-099**	
	N	**Anti-CS antibody GMC** EU/mL (95%CI)	**N**	**Anti-CS antibody GMC** EU/mL (95%CI)
One month after the third dose (month 3)	44	343 (276; 426)	198	369 (318; 428)
One month after the fourth dose (month 15)	37	235 (184; 300)	279	258 (235; 283)
One month after the fifth dose (month 27)	30	185 (140; 244)	291	177 (161; 195)
One month after the sixth dose (month 39)	33	182 (137; 241)	NA	NA

N= number of subjects-with available data (Per Protocol Set for immunogenicity – immuno sub-cohort)

NA = Not applicable

Immunogenicity against hepatitis B

The immunogenicity of Mosquirix following three doses has been evaluated in infants aged 8-12 weeks (at first dose). One month post-vaccination in the ATP cohort, 100% of the infants were seroprotected for hepatitis B (N=141). These infants did not receive any other hepatitis B antigen-containing vaccine.

In the Malaria-094 study, in which all subjects (aged 5-17 months) had previously received three documented doses of diphtheria, tetanus, pertussis, and hepatitis B vaccine, 100 % of the children were seroprotected for hepatitis B, 1 month after the third dose of Mosquirix and each revaccination (up to three annual revaccinations). Anti-HBs responses were boosted up until after the fourth dose, and remained stable thereafter.

Immunogenicity in special sub-populations

HIV infected children

In the Phase III efficacy study, children were not screened for HIV infection at enrolment.

Based on clinical data on 125 children with a confirmed HIV infection, Mosquirix elicited a lower anti-CS antibody response in HIV-infected children (GMC=193 EU/mL) as compared with children of unknown HIV infection status (GMC=492 EU/mL), one month after the third dose of Mosquirix.

In another clinical study, children with HIV infection stages 1 or 2, in the context of high treatment (anti-retrovirals and co-trimoxazole) coverage, were vaccinated with 3 doses of Mosquirix (N=99) or rabies vaccine (N=101). The anti-CS antibody GMC was 329 EU/mL one month after the third dose. Over 12 months of follow-up after the third dose of Mosquirix, VE against all episodes of clinical malaria was 37% (95% CI: -27; 69).

Preterm infants

The immunogenicity of Mosquirix in 362 preterm infants born after a gestation period of less than 37 weeks (median 36 weeks, with a range of 27 to 36 weeks), was evaluated one month after the third dose. The vaccine induced a similar anti-CS response in preterm infants (GMC=262 EU/mL) as compared to infants born after at least 37 weeks of gestation (GMC=247 EU/mL).

Low weight-for-age (malnourished) children

The immune response to CS protein was comparable for normal, low and very low weight-for-age children. The efficacy of Mosquirix is not expected to vary substantially according to weight-for-age.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and local tolerance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose, polysorbate 80, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate.

Suspension:
Dioleoyl phosphatidylcholine (DOPC), cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

After reconstitution:

Chemical and physical in-use stability has been demonstrated for 6 hours at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at 2 °C to 8 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

- Powder for 2 doses in a vial (type I glass) with a stopper (bromobutyl rubber), aluminium seal with a flip-off polypropylene cap;
- 1 mL suspension for 2 doses in a vial (type I glass) with a stopper (chlorobutyl rubber), aluminium seal with a flip-off polypropylene cap.

Mosquirix is available in a pack size of 50 vials of powder plus 50 vials of suspension.

6.6 Special precautions for disposal and other handling

The powder and suspension should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.

Mosquirix must be reconstituted prior to administration.

1. Withdraw the entire contents of the vial containing the suspension into the syringe.

2. Add the entire contents of the syringe into the vial containing the powder.

3. Shake gently until the powder is completely dissolved.

The reconstituted vaccine is an opalescent, colourless to pale brownish liquid.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.

After reconstitution, the vaccine should be used immediately; if this is not possible, the vaccine should be stored in a refrigerator (2 °C – 8 °C). If not used within 6 hours it should not be administered.

Each dose of 0.5 mL should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

A new needle should be used to administer each individual dose of the vaccine.

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

7. SCIENTIFIC OPINION HOLDER

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

8. SCIENTIFIC OPINION NUMBER(S)

EMEA/H/W/002300/001

9. DATE OF FIRST SCIENTIFIC OPINION/RENEWAL OF THE SCIENTIFIC OPINION

Data of first Scientific Opinion: 23 July 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)
GlaxoSmithKline Biologicals S.A.
Rue de l'institut 89
1330 Rixensart
Belgium

Name and address of the manufacturer(s) responsible for batch release

GlaxoSmithKline Biologicals S.A.
Rue de l'institut 89
1330 Rixensart
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

The CHMP recommends that batch compliance control of individual batches be performed before release on the market in third countries.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

- **Periodic safety update reports (PSURs)**

The scientific opinion holder shall submit the first PSUR for this product within 90 calendar days after the data lock point of 04/03/2016. Subsequently, the scientific opinion holder shall submit PSURs for this product every year until otherwise agreed by the CHMP.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Mosquirix powder and suspension for suspension for injection
Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 mL) contains 25 micrograms of RTS,S[1,2] adjuvanted with $AS01_E$[3].

[1] Portion of *P. falciparum* circumsporozoite protein fused with hepatitis B surface antigen (RTS), and combined with hepatitis B surface antigen (S)

[2] in the form of non-infectious virus-like particles (VLPs) produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

[3] $AS01_E$ adjuvant is composed of *Quillaja saponaria* Molina, fraction 21 (QS-21) (25 micrograms) and 3-O-desacyl-4'- monophosphoryl lipid A (MPL) (25 micrograms)

3. LIST OF EXCIPIENTS

Powder:
Sucrose, polysorbate 80, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate.

Suspension:
Dioleoyl phosphatidylcholine (DOPC), cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and suspension for suspension for injection

50 vials: powder (antigen)
50 vials: suspension (adjuvant)

50 x 2 doses (1 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Powder and suspension to be reconstituted before administration.

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

12. SCIENTIFIC OPINION NUMBER(S)

EMEA/H/W/002300/001

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
TWO-DOSE VIAL (POWDER)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mosquirix (RTS,S)
Powder for suspension for injection
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 doses (1 mL)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
TWO-DOSE VIAL (SUSPENSION)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mosquirix ($AS01_E$)
Suspension for suspension for injection
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 doses (1 mL)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Mosquirix

Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)

Read all of this leaflet carefully before your child starts receiving this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for your child only. Do not pass it on to others.
- If your child gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mosquirix is and what it is used for

Mosquirix is a vaccine that helps to protect against malaria caused by the parasite *Plasmodium falciparum*. Mosquirix also helps to protect your child against the hepatitis B virus, although it should not be used for this purpose only.
Mosquirix can be given to children aged from 6 weeks up to 17 months (at first dose).

Malaria is spread by the bite of an infected mosquito, which passes the malaria parasite into the bloodstream. Malaria is a serious illness with symptoms such as fever, headache, chills and vomiting. If not treated, malaria can progress to severe illness and death.

Hepatitis B is caused by the hepatitis B virus. It causes the liver to become swollen (inflamed).
In some people, the virus can stay in the body for a long time, and can eventually lead to serious liver problems, including liver cancer.

How the vaccine works:

- Mosquirix helps your child's body make its own protection. This will help protect your child against malaria and hepatitis B.

Important information about the protection provided:

- The vaccine does not provide complete protection against malaria caused by *P. falciparum* so your child might still become sick with malaria. In addition, the protection offered by Mosquirix will decrease over time. Therefore, it is important that you carry on with all other recommended malaria control measures (see below "*Protect your child from malaria*").
- Not all children who are vaccinated with Mosquirix will be protected against hepatitis B infection.
- Mosquirix will only protect against diseases caused by *P. falciparum* or hepatitis B virus.

Protect your child from malaria:

It is very important that you continue to take precautions to prevent your child from being bitten by mosquitoes:

- Make sure your child sleeps under a bed net treated with insecticide;
- Follow all other precautions as recommended by your doctor or nurse.

Seek medical care immediately if your child gets malaria symptoms.

2. What you need to know before your child receives Mosquirix

Mosquirix should not be given

- If your child is allergic to Mosquirix, hepatitis B vaccines or any of the other ingredients of this vaccine (listed in section 6).

Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

Warnings and precautions

Meningitis (an infection around the brain or spinal cord) has been reported rarely in clinical studies, after vaccination with Mosquirix.

Meningitis symptoms include fever, convulsions, vomiting, irritability, drowsiness, stiff neck, extreme sensitivity to bright light and bulging fontanelle (the soft spot on a baby's head).

See a doctor immediately if your child shows symptoms of meningitis.

Talk to your doctor or pharmacist before your child is given Mosquirix:

- if your child has a tendency to seizures/fits due to a fever, or if there is a history in the family of this. In this case, it is important that you ask your doctor or nurse what to do if your child has fever after being vaccinated with Mosquirix.
- if your child has a severe infection with a high temperature. In these cases, the vaccination may be postponed until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- if your child has a bleeding problem or bruises easily;
- if your child has breathing difficulties, please contact your doctor. This may be more common in the first three days following vaccination if your child was born prematurely (before or at 28 weeks of pregnancy).

Children with a weakened immune system, for example due to HIV infection or due to medicines that suppress the immune system, may not get the full benefit from Mosquirix.

Other medicines and Mosquirix

Tell your doctor if your child is taking, has recently taken or might take any other medicines, or has recently received any other vaccine.

Mosquirix can be given at the same time as other vaccines. A different injection site will be used for each type of vaccine.

Mosquirix can be given in combination with Seasonal Malaria Chemoprevention.

Mosquirix contains polysorbate 80, sodium and potassium

This vaccine contains 0.03 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions. Tell your doctor if your child has any known allergies.

This vaccine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Mosquirix is given

The doctor or nurse will give the recommended dose of Mosquirix to your child. The first dose can be given from the age of 6 weeks up to 17 months.

Usually, your child will receive three doses of Mosquirix with an interval of one month between doses. After these first three doses, in accordance with local recommendations, your child might receive a fourth dose from 12 months to 18 months after the third dose.

Annual revaccination until 5 years of age may be recommended after the fourth dose.

You will be informed when your child should come back for the next dose of Mosquirix.

Mosquirix is given as an injection of 0.5 mL into a muscle.

If your child misses a dose

If your child misses a scheduled dose, make sure he/she finishes the complete vaccination course. This will maximise the protection offered by Mosquirix.

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

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Very common (these may occur with more than 1 in 10 doses of the vaccine):

- irritability
- fever
- swelling, redness and pain where the injection was given

Common (these may occur with up to 1 in 10 doses of the vaccine)

- decreased appetite
- drowsiness
- diarrhoea

Uncommon (these may occur with up to 1 in 100 doses of the vaccine):

- convulsions or fits due to fever (within 7 days after vaccination)
- vomiting
- hard lump where the injection was given

Decreased appetite can occur more frequently (very common) after the fourth dose than after the other doses of Mosquirix. All other adverse reactions occur at the same or lower frequency.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Reporting of side effects

If your child gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mosquirix

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

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

Store in a refrigerator (2 °C – 8 °C).
Store in the original package in order to protect from light.
Do not freeze.

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 Mosquirix contains

Each vaccine dose contains 25 micrograms of RTS,S with the $AS01_E$ adjuvant.

RTS,S contains a small amount of the 'outer coatings' of the *P. falciparum* malaria parasite and of the hepatitis B virus. These 'outer coatings' are not infectious and cannot make your child ill.
Adjuvants are used to improve the body's response to the vaccine.

The other ingredients are:

Powder
Sucrose, polysorbate 80, disodium phosphate dihydrate and sodium dihydrogen phosphate dihydrate.

Suspension
Dioleoyl phosphatidylcholine, cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate and water for injections.

What Mosquirix looks like and contents of the pack

Powder and suspension for suspension for injection.

The powder is white.
The suspension is an opalescent, colourless to pale brownish liquid.

One pack of Mosquirix consists of:

- 50 vials containing powder for 2 doses
- 50 vials containing 1 mL of suspension for 2 doses

Scientific Opinion Holder and Manufacturer

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

The powder and suspension should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.

Mosquirix must be reconstituted prior to administration.

1. Withdraw the entire contents of the vial containing the suspension into the syringe.
2. Add the entire contents of the syringe into the vial containing the powder.
3. Shake gently until the powder is completely dissolved.

The reconstituted vaccine is an opalescent, colourless to pale brownish liquid.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.

After reconstitution, the vaccine should be used immediately; if this is not possible, the vaccine should be stored in a refrigerator (2 °C – 8 °C). If not used within 6 hours it should not be administered.

Each dose of 0.5 mL should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

A new needle should be used to administer each individual dose of the vaccine.

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