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 [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] AS01E adjuvant is composed of *Quillaja saponaria* Molina, fraction 21 (QS-21) (25 micrograms) and 3-O-desacyl-4'- monophosphoryl lipid A (MPL) (25 micrograms)
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 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 18 months after the third dose.

Other paediatric population:
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.

Sodium and Potassium content

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 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

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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

Adverse reactions after 3 doses

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 3 doses of Mosquirix.

Adverse reactions reported are listed according to the

following frequency: Very common ≥ 1/10
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1000 to < 1/100

Table 1: Adverse reactions reported after 3 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%.

Adverse reactions after the 4th dose

Clinical data in more than 4200 children who received a fourth dose of Mosquirix shows that, following this dose, decreased appetite was reported more frequently (very common) compared to the rates observed after the first three doses. All other adverse reactions occurred at the same or lower frequency as reported in Table 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

In a Phase III randomized 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 4200 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: Vaccine efficacy in infants aged 6-12 weeks at first dose

	Vaccine efficacy against all episodes ofclinical malaria (95% CI)	**Vaccine efficacy against severe malaria** (95% CI)	**Vaccine efficacy against hospitalisation caused by malaria** (95% CI)
Over 12 months follow-upfrom dose 3 (ATP* cohort, N = 6003)	33% (26; 39)	37% (5; 58)	32% (7; 50)
Over 18 months follow-upfrom dose 3 (ATP* cohort, N=6003)	27% (20; 32)	15% (-20; 39)	17% (-7; 36)
	3 doses only (ATP* cohort, N=5997)		
Over 30 months follow-upfrom dose 3	20% (13; 27)	11% (-22; 35)	10% (-15; 30)
Over 36 months follow-upfrom dose 3**	18% (11; 25)	13% (-17; 35)	13% (-9; 31)
	3 doses + 4th dose (ATP* cohort, N=5997)		
Over 30 months follow-upfrom dose 3	28% (22; 34)	17% (-14; 40)	25% (3; 42)
Over 36 months follow-upfrom 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 offollow-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 whoreceived three doses only or three doses plus a fourth dose, is given in Table 3.

Table 3: 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=6918)			
Over 30 months follow-up from dose 3	34% (29; 39)	2% (-28; 25)	18% (1; 32)
Over 46 months follow-upfrom dose 3**	26% (21; 31)	-6% (-35; 17)	12% (-5; 26)
3 doses + 4th dose (ATP* cohort, N=6918)			
Over 30 months follow-up from dose 3	46% (42; 50)	32% (10; 50)	40% (26; 52)
Over 46 months follow-upfrom 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. 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: 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= 1905)		
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= 2512).		
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

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 5.

Table 5: 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

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.

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

36 months
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.

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

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

- 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. Marketing authorizatoion holder and manufacturing site addresses

Marketing authorization holder:
GlaxoSmithKline
Biologicals S.A. Rue de
l'Institut 89

Manufacturing site address:

manufacturer	Responsibilities
GlaxoSmithKline biologicals S.A.S 637 rue des Aulnois, 59230 saint-amand-les-eaux, France.	formulation
GlaxoSmithKline biologicals S.A.S 637 rue des Aulnois, 59230 saint-amand-les-eaux, France.	Filling and lyophilisation
	Labelling/packaging operations
GlaxoSmithKline biologicals S.A. parc de la Noire Epine, Avenue fleming 20-1300 wavre; Belgium	QC testing
GlaxoSmithKline biologicals S.A.S 637 rue des Aulnois,59230 saint-amand-les-faux,France.	QC testing
GlaxoSmithKline biologicals S.A. 89, rue de I'lstitut-1330 rixensart; belgium	QC testing

8. Marketing authorization number:
CTD10410

9. Date of first registration revision:
21/03/2023

10. Date of revision of the text:
14/09/2023

11. Dosimetry:
Not applicable

12. Instructions for Preparation of Radiopharmaceuticals
Not applicable