1 NAME OF THE MEDICINAL PRODUCT

CYVAC,
R21 Malaria Vaccine (Recombinant, Adjuvanted)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 mL contains
[1, 2] R21 Malaria Antigen: 5 mcg
[3] Matrix-M1 (Adjuvant): 50 mcg

[1] Portion of *P. falciparum* circumsporozoite protein fused with hepatitis B surface antigen

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

[3] Matrix-M1 adjuvant is composed of Matrix-A (85 parts) and Matrix-C (15 parts) with phospholipid and cholesterol.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection
The solution is clear, colourless to mildly turbid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

R21 Malaria Vaccine (Recombinant, Adjuvanted) is indicated for active immunization of children aged 5 to 36 months against Malaria caused by *Plasmodium falciparum*.

The use of R21 Malaria Vaccine (Recombinant, Adjuvanted) 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 5 months of age up to 36 months of age (at first dose):

- Three doses, each of 5 mcg R21 and 50 mcg Matrix-M1 should be given at monthly intervals.
- A fourth dose is recommended 12 months after the third dose.

Method of administration

Administration of the vaccine is by intramuscular injection.

The anterolateral thigh is the preferred site for injection in children below 24 months age, while deltoid muscle is the preferred site for injection in children above 24 months of age. However, vaccine can be administered in anterolateral thigh intramuscularly in children above 24 months of age, if there is no sufficient bulk of muscle at deltoid site.

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 R21 Malaria Vaccine (Recombinant, Adjuvanted) Or Hepatitis B vaccines.

4.4 Special warnings and special 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 undertake a review of the vaccinee's medical history (especially with regard to previous vaccination and possible occurrence of side effects) and a clinical examination.

As with other vaccines, vaccination with R21 Malaria Vaccine (Recombinant, Adjuvanted) 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 use of R21 Malaria Vaccine (Recombinant, Adjuvanted) vaccination.
In case of fever antipyretic measures should be initiated according to local guidelines.

Fever may follow each dose of R21 Malaria Vaccine (Recombinant, Adjuvanted) (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 R21 Malaria Vaccine (Recombinant, Adjuvanted), the routine use of prophylactic antipyretic medicinal products before vaccination is therefore not recommended.

Protection against P. falciparum malaria

R21 Malaria Vaccine (Recombinant, Adjuvanted) 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.

R21 Malaria Vaccine (Recombinant, Adjuvanted) 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.

Systemic immunosuppressive medications and immunodeficiency

There are no data in children receiving immunosuppressive treatment or children with immunodeficiencies. In these children, it cannot be ruled out that efficacy is impaired.

Precautions for use
Do not administer the vaccine intravascularly, intradermally or subcutaneously.

Patients at risk of bleeding
As with other vaccines administered intramuscularly, R21 Malaria Vaccine (Recombinant, Adjuvanted) 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
In a phase Ib study (NCT05155579), immunogenicity of R21/Matrix-M was evaluated when co-administered with EPI vaccines. There was no significant difference in the magnitude of the anti-NANP IgG response to R21 when co-administered with Measles-Rubella and Yellow fever vaccine given at 9 months of age. Also, the seroconversion rates to Measles and Rubella were similar in participants who received R21 vaccine along with Measles-rubella vaccine compared to the participants who received R21 vaccine alone. Thus, there was no interference when R21 was given with the Measles-Rubella vaccine.
If R21 Malaria Vaccine (Recombinant, Adjuvanted) has to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

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

R21 Malaria Vaccine (Recombinant, Adjuvanted) 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

Across over 3200 children participating in a four country phase III trial in Africa after four doses of the R21 Malaria Vaccine/Matrix-M1 the most commonly reported systemic adverse reactions were fever (46.7%), loss of appetite (3.7%), drowsiness (2.5%) and local injection site reactions such as pain (18.6%) and swelling (4.1%).
In this study, the most common serious adverse event associated with R21 malaria vaccine was febrile convulsions (within 7 days post-vaccination) (0.15 %).

Adverse reactions after 4 doses

The safety profile presented below is based on an analysis of more than 3,200 children who have been vaccinated in clinical studies with 4 doses of R21 Malaria Vaccine/Matrix-M1.

Adverse events are organized by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness.

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 4 doses of the vaccine

System Organ Class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Common	decreased appetite
Psychiatric disorders	Common	irritability
Nervous system disorders	Common	drowsiness
	Uncommon	Febrile convulsions (within 7 days post-vaccination)
Gastrointestinal disorders	Uncommon	diarrhoea
General disorders and administration site conditions	Very common	fever
	Very common	injection site pain
	Common	Injection site swelling

	Common	injection site redness

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: Parasitic vaccines, ATC code: J07XA

Mechanism of action

R21 Malaria Vaccine (Recombinant, Adjuvanted) is a pre-erythrocytic vaccine intended to limit the ability of *Plasmodium falciparum* to infect, mature and multiply in the liver by eliciting predominantly immunity to the circumsporozoite (CS) protein present at the surface of the sporozoite.

Vaccine efficacy

In a Phase III randomized controlled double-blind study, VAC078, conducted at 5 sites in 4 sub-Saharan African countries, Burkina Faso, Mali, Tanzania and Kenya with a wide range of transmission intensities (https://clinicaltrials.gov/ct2/show/NCT04704830), more than 4,800 children from 5-36 months of age were enrolled to evaluate efficacy and safety of R21 Malaria Vaccine/Matrix-M1 when given according to a 0, 1, 2-month schedule. In addition, these children received per protocol a fourth dose (booster), administered 12 months after the third dose.

The efficacy of the vaccine was evaluated in the context of high insecticide treated bed nets coverage, and substantial seasonal malaria chemoprevention use at west African sites of high malaria transmission. The trial included two sites of highly seasonal malaria transmission and

three sites with more perennial transmission ("standard" sites in Kenya, Tanzania and Dande, Burkina Faso).

The primary objective of the study was efficacy against the first or only episode of clinical malaria over a follow-up period of 12 months after three doses in each age group.
In the recent analysis, 4719 subjects were followed up from 2 weeks after their third vaccine dose and 4644 were considered as modified per protocol population (mPP) analysis. Overall, 4505 participants (97%) completed the 12 month follow-up with 98 % (2286 participants out of 2339) at seasonal and 96 % (2219 participants out of 2305) at standard sites completing the 12-month follow-up.
95.6 % (2229 participants out of 2339) at seasonal follow-up completed the 18 month-follow-up after 3rd vaccine dose.
In the primary analysis of efficacy, seasonal and standard sites were analysed separately. The modified per protocol population was the SAP-pre-specified population for the primary analysis.
VE at 12 months following the primary series of vaccinations (primary case definition): Efficacy against clinical malaria (time to first event analysis) over a follow-up period of 12 months post dose 3 was 75% (71-79%) at seasonal sites and 68% (61-74%) at standard sites. When combining all sites, VE (time to first event analysis) was 73% [70-76].
When assessing VE against all clinical malaria episodes, VE was 75% [71-78] at the seasonal sites and 67% [59-73] at the standard vaccination regime sites. When combining all sites, VE was 72% [69-75].
VE (primary case definition) at 6 months following the booster vaccination 75% [71-79] at the seasonal sites. VE against all clinical malaria episodes was 70% [66-73] at the seasonal sites. At 18 months following the primary series of vaccinations, VE was 73% [70-77] when assessing time to first clinical malaria episode at the seasonal sites and 72% [68-75] when assessing all clinical malaria episodes.

The phase III trial results were consistent with an ongoing single site phase IIb trial, VAC076,

at Nanoro, Burkina Faso (https://clinicaltrials.gov/ct2/show/NCT03896724) which, with the same immunisation regime (three primary series doses plus a booster dose at 12 months) observed 76%, 77% and 73% efficacy over one, two and three years of follow-up, respectively. Safety findings were similar to the phase III trial (above).

The first trial in Africa of the R21 Malaria Vaccine/Matrix M1 took place in Kilifi, Kenya (VAC073) assessing the safety and immunogenicity of several R21 Malaria Vaccine/Matrix M1 dosing regimes in 92 subjects, was an age de-escalation dose escalation trial in adults, children and infants (https://clinicaltrials.gov/ct2/show/NCT03580824). The vaccine was well tolerated and immunogenic in all age groups, and most immunogenic in infants administered the 5 mcg R21 with 50 mcg Matrix M1 formulation later used in the phase III trial.

One safety and efficacy trial, VAC072, was undertaken of the R21 Malaria Vaccine/Matrix M1 in the United Kingdom using a well-studied human challenge protocol with infectious mosquito bites (https://clinicaltrials.gov/ct2/show/NCT03970993). The vaccine was well tolerated and immunogenic at a range of dose levels and particularly high efficacy was observed, of 75%, using a low dose regimen of 10 mcg R21 in 50 mcg of Matrix-M1 adjuvant.

In summary, R21 Malaria Vaccine/Matrix M1 has shown a well-tolerated safety profile in four trials enrolling over 5350 subjects in five countries. Efficacy of the vaccine reached 75% in a phase IIa, a phase IIb and a recent phase III trial in the first year of follow-up. In the phase IIb trial this efficacy has been followed for three years and appeared well-maintained (at 73% efficacy) over this time period with a single booster dose at the end of the first year.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

A repeat dose toxicity study conducted on R21/Matrix-M1 in BALB/c mice (4 dose regimen) revealed no special hazard for humans. There were no unscheduled deaths in the study. There were no clinical signs considered related to treatment and there was no apparent reaction to

treatment at the dose site. It was concluded that the administration of R21 combined with Matrix M adjuvant was well tolerated and was not associated with any systemic toxicological changes. All related changes were consistent with the expected immune stimulation associated with the administration of a vaccine with or without adjuvant or with minimal inflammatory changes in the muscle injection sites.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adjuvant (Matrix-M1) (Matrix-A + Matrix-C)
Magnesium chloride
Sucrose
Tris Buffer
Phosphate Buffered Saline

6.2 Incompatibilities

The vaccine is not to be mixed with other vaccines/ products in the same syringe.

6.3 Shelf-life

Unopened vial: 24 months

Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +8ºC. All opened multidose vials of R21 Malaria Vaccine (Recombinant, Adjuvanted) should be discarded at the end of immunization session or within six hours, whichever comes first.

6.4 Special precautions for storage

Store in a refrigerator (+2° to +8°C).

Do not freeze.

Store in an original package in order to protect from light. For storage condition, after first opening of the medicinal product, see Section 6.3.

6.5 Nature and contents of container

One dose

Multidose vials (Two doses)

6.6 Special Precautions for Disposal and Other Handling

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

7 MARKETING AUTHORIZATION

Serum Institute of India Pvt. Ltd.
212/2, Hadapsar, Pune-411028, INDIA.

8 MARKETING AUTHORISATION NUMBER (S)

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9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT
