SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

Measles Rubella Cipla - Powder and diluent for solution for Injection

Measles and rubella vaccine (live)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0,5 ml) contains:

Measles virus[1] (Edmonston Zagreb strain) (live attenuated): not less than 1000 $CCID_{50}$[2]

Rubella virus[1] (Wistar RA 27/3 strain) (live attenuated): not less than 1000 $CCID_{50}$[2]

[1] produced in human diploid (MRC-5) cells.

[2] 50 % of a cell culture infectious dose.

This vaccine may contain traces of neomycin sulphate. **See section 4.3**.

Excipient with known effect: Each dose contains 25 mg of sorbitol. For the full list of excipients, **see section 6.1**.

3 PHARMACEUTICAL FORM

Powder and diluent for solution for injection.

The freeze-dried vaccine powder is a yellowish-white friable mass and the diluent for reconstitution is a clear colourless liquid.

The diluent is free from visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Measles Rubella Cipla is indicated for:

- active immunisation against measles and rubella in infants and children from the age of 9 months and older, adolescents and young adults at risk;

- immunisation of susceptible non-pregnant adolescent and adult females of childbearing age is indicated if certain precautions are observed.

4.2 Posology and method of administration

Posology

The dose for all ages is the same; being a single dose of 0,5 mL of reconstituted vaccine. The reconstituted vaccine is a yellowish to a pale yellow clear liquid.

For instructions on the reconstitution of the vaccine before administration, see **section 6.6**.

Vaccination schedule

The national immunisation guidelines need to be referred to before administration of Measles Rubella Cipla.

Measles:

All children should receive 2 doses of measles-containing vaccine.

Depending on the risk of measles infection; one of the following immunisation schedules is to be followed:

- If the risk of measles infection is high, the first dose of Measles Rubella Cipla should be administered at 9 months or shortly thereafter and the second dose should be administered between 15 and 18 months.

The minimum interval between doses is 4 weeks.

- If the risk of measles infection is low, the first dose of Measles Rubella Cipla may be administered between 12 to 15 months and the second dose may be administered between 4 to 6 years of age.

Rubella:

All children should receive at least one dose of rubella-containing vaccine. It is given as a combination with measles-containing vaccine with first dose usually given at 9 months or 12 to 15 months and a second dose at 15 to 18 months or 4 to 6 years.

Susceptible non-pregnant adolescent and adult females of childbearing age may receive one dose of Measles Rubella Cipla if certain precautions are observed (see **section 4.3**).

Method of administration

A separate sterile needle and syringe is to be used for each patient. Before administration of Measles Rubella Cipla, the skin over the site to be injected should be cleaned and allowed to dry. The vaccine should be administered as a deep subcutaneous injection. The anterolateral thigh is the preferred site for injection in

infants younger than 12 months. The outer triceps area of the upper arm is the preferred site for injection in persons 12 months or older.

DO NOT INJECT INTRAVASCULARLY.

(see **section 4.4** Special warnings and precautions for use).

For instructions on reconstitution of Measles Rubella Cipla before administration see section 6.6 to confirm the vaccine's integrity.

4.3 Contraindications

Measles Rubella Cipla is contraindicated in recipients who:

- have had a previous confirmed anaphylactic reaction to a previous dose of a vaccine containing the same antigens or are hypersensitive to any of the vaccine components, including gelatin. (see **section 6.1**);
- are allergic to neomycin; as Measles Rubella Cipla may contain traces of this antibiotic.
- are allergic to cow's milk as there have been a few reports of hypersensitivity with MMR vaccines in these individuals;
- are severely immunosuppressed because of medication (e.g. high dose steroids, alkylating agents and antimetabolites), other therapy such as radiation, or underlying illness (e.g congenital immunodeficiency, leukaemia, lymphoma, generalised malignant disease) or patients with HIV infection who are severely immunocompromised or patients with a family history of altered immunocompetence;
- pregnant, due to the theoretical, but never demonstrated teratogenic risk (see **section 4.6**);

- have received immunoglobulins or blood products (see **sections 4.4 and 4.5**).

Measles-containing vaccines such as Measles Rubella Cipla should not be administered to patients with concurrent moderate or severe illnesses, including those with significant fever.

There is no evidence that measles or rubella vaccine will suppress the immune system enough to activate latent tuberculosis or augment active tuberculous disease. However, persons with known active tuberculosis should not be vaccinated until treatment has been established.

Low grade fever, mild respiratory infections or diarrhoea, and other minor illness should not be considered as contraindications. It is particularly important to immunise children with malnutrition.

4.4 Special warnings and precautions for use

- Measles Rubella Cipla is to be administered by subcutaneous route only;
- After administration of Measles Rubella Cipla; the recipient should remain under observation for at least 30 minutes for possibility of occurrence of rapid allergic reactions;
- Adequate treatment provisions, including epinephrine (adrenalin) injection (1:1000), should be available for immediate use should an anaphylactic or anaphylactoid reaction occur;
- Patients with rare hereditary conditions of sorbitol intolerance should not be vaccinated with Measles Rubella Cipla;
- Immunocompromised patients (whether from disease or treatment) may not develop an optimal immune response after vaccination with Measles Rubella Cipla;
- Measles Rubella Cipla may be used in children with known or suspected HIV infection and who are not severely immunosuppressed;
- For persons with moderate or severe illness, vaccination with Measles Rubella Cipla should be postponed and administered after the patient has recovered;
- Vaccination should be deferred for 3 months or longer following blood or plasma transfusions, or administration of immunoglobulins (see **section 4.5**);
- In order to improve the traceability of vaccines, the name and batch number of the administered product should be clearly recorded.
- Persons who have had an anaphylactic reaction to gelatin or gelatin-containing products should be evaluated by an allergist prior to receiving gelatin-containing vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Patients receiving immunosuppressant therapy, including anti- neoplastics or therapeutic doses of corticosteroids may display a reduced response to Measles Rubella Cipla.

Measles Rubella Cipla should not be administered for at least 3 months after the use of immunoglobulins or blood products containing immunoglobulins due to the risk of vaccine inactivation. For the same reason, immunoglobulins or blood products should not be administered within two weeks after vaccination.

Tuberculin positive individuals may transitionally become tuberculin negative after vaccination.

Measles Rubella Cipla can be safely and effectively given simultaneously with DTP, DT, TT, Td, BCG, Polio vaccine (OPV and IPV), *Haemophilus influenzae* type b, Hepatitis B, Yellow fever vaccine and vitamin A supplementation.

4.6 Fertility, pregnancy and lactation

Pregnancy

Measles Rubella Cipla is contraindicated (see **section 4.3**) in pregnancy.

Breastfeeding

No studies on the effects on lactation have been performed.

Fertility

No human data on the effect of Measles Rubella Cipla on fertility are available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use of machines have been performed.

4.8 Undesirable effects

a. Summary of the safety profile

The type and rate of severe adverse reactions do not differ significantly from the measles and rubella vaccine reactions described separately.

The measles vaccine may cause within 24 hours of vaccination mild pain and tenderness at the injection site. In most cases these reactions spontaneously resolve within two to three days without further medical attention. A mild fever can occur in 5 to15 % of vaccinees seven to twelve days after vaccination and last for one to two days. Rash occurs in approximately 2 % of recipients, usually starting seven to ten days after vaccination and lasting two days.

The mild side effects occur less frequently after the second dose of a measles-containing vaccine and tend to occur only in persons not protected by the first dose. Encephalitis has been reported following measles vaccination at a frequency of approximately one case per million doses administered although a causal link is not proven.

The rubella component may commonly result in joint symptoms manifested as arthralgias (25 %) and arthritis (10 %) among adolescents and adult females that usually last from a few days to two weeks. Symptoms typically begin one to three weeks after vaccination and last one day to two weeks. These transient reactions seem to occur in non-immunes only, for whom the vaccine is important. Low grade fever and rash, lymphadenopathy, myalgia and paraesthesiae are commonly reported.
Thrombocytopenia is rare and has been reported in less than one case per 30 000 doses administered. Anaphylactic reactions are also rare. In susceptible individuals the vaccine may very rarely cause allergic reactions like urticaria, pruritis and allergic rash within 24 hours of vaccination. Clinical experience has exceptionally recorded isolated reactions involving the Central Nervous System (CNS). These more serious reactions have however, not been directly linked to vaccination.

Adverse reactions from clinical trials

Frequencies are reported as:

Very common; ≥ 1/10

Common; ≥ 1/100 to < 1/10

Uncommon: ≥ 1/1 000 to < 1/100

Very rare: ≤ 1/10 000

Frequency not known (cannot be estimated from the available data)

In controlled clinical studies, signs and symptoms were monitored during a 5 to 6 week follow-up period (trial specific). The safety profile presented below is based on a total of 1444 subjects administered Measles Rubella Cipla in clinical trials. This data is further supported by other clinical study reports.

Table 1: Clinical Trial data

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system	*Uncommon*	Cervical adenitis/
		Lymphadenopathy
Eye Disorders	*Common*	Red eyes
Respiratory, thoracic and mediastinal disorders	*Common*	Coryza and cold
Skin and subcutaneous tissue disorders	*Uncommon*	Rash
Musculoskeletal and connective tissue disorder	*Common*	Arthralgia
	Uncommon	Arthritis
General disorders and administrative site conditions	*Common*	Fever
		Local pain & swelling
		Redness and tenderness
		Induration
		Nodule at injection site

Adverse reactions from spontaneous reporting and data from sources other than clinical trials/studies data

The following side-effects have been reported with the use of vaccines containing measles and rubella viruses; including Measles Rubella Cipla:

Table 2: Adverse reactions from spontaneous reporting and other sources

System Organ Class	Frequency	Adverse reactions
Infections and Infestations	*Less frequent*	Atypical measles syndrome
		Encephalomyelitis
		Aseptic meningitis
		Acute disseminated encephalomyelitis
		Septic shock
Blood and lymphatic system disorders	*Frequent*	Lymphadenopathy
	Less frequent	Thrombocytopenia
		Idiopathic thrombocytopenia
Immune system disorders	*Less frequent*	Hypersensitivity
		Anaphylactic/ Anaphylactoid Reactions (urticaria, angio-neurotic oedema, wheezing, hypotension, hives and shock)
Nervous system Disorders	*Frequent*	Headache
		Paraesthesia
		Polyneuropathy
	Frequency unknown	Acute flaccid paralysis
	Less frequent	Encephalitis
		Encephalomyelitis
		Encephalopathy

		Subacute sclerosing panencephalitis
		Optic neuritis
		Seizures/ convulsion
		Febrile convulsion
		Afebrile seizure
		Syncope
	Frequency Unknown	Guillain-Barré Syndrome
		Transverse myelitis
Ear and labyrinth disorders	*Less frequent*	Sensorineural hearing loss
Respiratory, thoracic and mediastinal disorders	*Frequent*	Pharyngitis
		Sore throat
	Less frequent	Cough
Gastrointestinal disorders	*Less frequent*	Diarrhoea
		Vomiting
Skin and subcutaneous tissue disorders	*Frequent*	Rash
	Less frequent	Allergic reactions like urticaria, pruritis and allergic rash
	Frequency Unknown	Stevens-Johnson Syndrome
Musculoskeletal and connective tissue disorders	*Frequent*	Myalgia
	Less frequent	Arthralgia
		Arthritis
General disorders and administration site condition	*Frequent*	Fever
		Malaise
		Mild pain and tenderness
		Swelling
		Induration
		Sterile abscess at the injection site
		Febrile seizure/ febrile convulsion
		Discomfort

Injury, poisoning and procedural complications	*Frequent*	Immunisation anxiety-related reaction

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be different from adults, largely due to the difference in the maturity of the immune system between children and adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions: to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8, and to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9 Overdose

No cases of overdose have been reported for Measles Rubella Cipla.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Viral vaccine, ATC code: J07BD53

Measles Rubella Cipla is a mixture of live attenuated measles and rubella viruses which stimulates active immunity to measles and rubella by inducing the production of IgM and IgG antibodies.

Clinical studies have shown that Measles Rubella Cipla is immunogenic and generally, well tolerated.

Immunogenicity and safety in recipients of various age groups have been established in the following several clinical trials:

In **study 01:** 1360 prepubertal and adolescent girls received a single dose of Measles Rubella Cipla. All subjects tested in the immunogenicity study were seropositive for IgG antibodies 8 weeks post vaccination.

In **study 02:** 84 children ages 4 to 12 years received a single dose of Measles Rubella Cipla. 96,43 % of subjects were seropositive for IgG measles antibodies and 91,67 % of subjects were seropositive for IgG rubella antibodies 6 to 8 weeks post vaccination. The difference between pre-immunisation and post- vaccination. The difference between pre-immunisation and post- immunisation IgG levels for measles and rubella was statistically significant.

In **study 03:** a total of 867 000 doses of Measles Rubella Cipla were administered to children of 1 to 14 years of age in a mass immunisation campaign in Albania in 2000. The number of measles cases dropped from 2386 in 1997 to 18 cases in 2001. In cases of rubella, the same was reduced from 721 cases in 1998 to 10 cases in 2001.

In **study 04**: a total of 4, 853, 233 individuals of 8 to16 years of age were administered a dose of Measles Rubella Cipla in a mass immunisation campaign in South Korea in 2001.
As a result, in 2006, the interruption of indigenous measles transmission was achieved and measles elimination was declared in that country.

In **study 05**: more than 33 million doses of Measles Rubella Cipla were administered to individuals from 5 to 25 years of age in a mass immunisation campaign in Iran in 2003. Simultaneously, a study was conducted in 1 940 individuals vaccinated during the campaign across the country to evaluate immunity against rubella vaccine using a cluster sampling design. 61,9 % of vaccinees were immune to rubella before vaccination while 38,1 % were susceptible to rubella before vaccination. At the end

of a month, 98 % of the susceptible group acquired immunity to rubella after vaccination. The conclusion was that vaccination provided appropriate immune coverage among vaccinees. Also, rubella vaccine induced favourable immunity in a part of the of the childbearing female (15 to 25 years) population, which could prevent congenital rubella syndrome among those females.

In **study 06**: a clinical trial in Vietnam in 2016 was conducted comparing a locally manufactured measles and rubella vaccine against Measles Rubella Cipla in individuals from 1 to 2 years, 2 to 18 years and 18 to 45 years.
A serological response of more than a 2-fold increase in titres against measles was noted in 100 % who were previously seronegative and 28 % who were previously seropositive in the Measles Rubella Cipla group.

Similarly, a serological response of more than a 2-fold increase in titres against rubella were noted in 99,3 % who were previously seronegative and 4,5 % who were previously seropositive in the Measles Rubella Cipla group.

5.2 Pharmacokinetic properties

An evaluation of pharmacokinetics in vaccines is not necessary.

5.3 Preclinical safety data

No formal animal testing has been carried out for non-clinical assessment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Partially hydrolysed Gelatine

Sorbitol

L-Histidine

L-Alanine

Tricine

L-Arginine Hydrochloride

Lactalbumin Hydrolysate

Minimum Essential Medium

Diluent:

Sterile Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products, except for the recommended diluent (sterile Water for injection) mentioned in **section 6.6.**

6.3 Shelf life

Vaccine powder for injection: 30 months; if stored in a refrigerator at a temperature between 2 ºC to 8 ºC and protected from light.

Diluent: 5 years when stored at or below 30 ºC.

Reconstituted vaccine: Store for no longer than 6 hours in a refrigerator at a temperature between 2 ºC to 8 ºC and protected from light.

6.4 Special precautions for storage

Vaccine: Store in a refrigerator at a temperature between 2 ºC and 8 ºC and PROTECT FROM LIGHT. Store in the original package.

Diluent: Store at or below 30 ºC, DO NOT FREEZE.

For storage conditions of the reconstituted vaccine, see **section 6.3.**

6.5 Nature and contents of container

Powder for injection:

Single dose presentation

- Yellowish white powder for injection in an amber vial (type 1 glass) with a stopper (grey

bromobutyl rubber), with a violet aluminium overseal.

50 individual vials packed into a labelled box with 50 leaflets.

Ten dose presentation

- Yellowish white powder for injection in an amber vial (type 1 glass) with a stopper (grey bromobutyl rubber), with a violet aluminium overseal.

50 individual vials are packed into a labelled box with 50 leaflets.

Diluent for reconstitution:

Single dose presentation

0,5 mL clear colourless liquid in a colourless ampoule (type 1 glass).

10 x 0,5 mL ampoules are placed in thermoformed tray (PVC). Aluminium foil acting as a lidding foil for clear transparent blister tray (PVC) with aluminium printed foil consisting of 10 ampoules. Such 5 trays are packed into a labelled box.

Ten dose presentation

5 mL clear colourless liquid in a colourless ampoule (type 1 glass).

10 x 5 mL ampoules are placed in thermoformed tray (PVC). Aluminium foil acting as a lidding foil for clear transparent blister tray (PVC) with aluminium printed foil consisting of 10 ampoules. Such 5 trays are packed into a labelled box.

6.6 Special precautions for disposal and other handling

Vaccine vial monitor:

A vaccine vial monitor is attached to the vial cap. This time- temperature sensitive label provides an indication of the cumulative heat to which the vial has been exposed and warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

Before using the vaccine, interpret the vaccine vial monitor; a circle with a small square inside it. (See Figure 1 below).

Focus on the inner square. The combined effects of time and temperature cause this inner square to

darken gradually and irreversibly. As long as the colour of this square is lighter than the colour of the outer circle, the vaccine can be used. As soon as the colour of the inner square becomes the same colour as the outer circle or a darker colour than the outer circle; then the vial should be discarded.

Figure 1: Reading a Vaccine Vial Monitor

Inner square lighter than outer circle.

If the expiry date has not passed, USE the vaccine.

At a later time, inner square still lighter than outer circle.

If the expiry date has not been passed, USE the vaccine.

Discard point:

Inner square matches colour of outer circle. **DO NOT use the vaccine**.

Beyond the discard point:

Inner square darker than outer ring. **DO NOT use the vaccine.**

Discard the vial monitor label prior to reconstitution of the vaccine.

Diluent or reconstituted vaccine which has been exposed to freezing should not be used.

The diluent and reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspects prior to administration. In the event of either being observed, discard the diluent or reconstituted vaccine.

Instructions for reconstitution of the vaccine:

The diluent supplied for reconstitution is specially designed for use with Measles Rubella Cipla. Only the supplied diluent (Sterile Water for Injection) is to be used to reconstitute the vaccine. The vaccine should be reconstituted with the entire diluent supplied using a sterile syringe and needle. With gentle rotation of the vial, the dried cake dissolves. The reconstituted vaccine is a yellowish to pale yellow clear liquid. Withdraw 0,5 ml of reconstituted solution into the syringe; now ready for administration. A new needle should be used to administer the vaccine. For instructions on administration, see **section 4.2**.

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

All used injection equipment should be placed in a sharp's disposal container or safety box immediately after use to prevent needle stick injury or reuse.

7 HOLDER OF CERTIFCATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap,

Mispel Street,

Belville, 7530

Customer Care: 080 222 6662

8 REGISTRATION NUMBER

55/30.2/0426

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

May 2023

10 DATE OF REVISION OF THE TEXT

Not applicable