Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Proper name: measles, mumps, and rubella virus vaccine, live, attenuated, Merck Std.

Product Characteristics: M-M-R® II with rHA (recombinant human albumin) is a sterile lyophilized preparation combining three viruses: (1) Measles Virus Live, a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo, (2) Mumps Virus Live, the attenuated Jeryl Lynn® strain of mumps virus grown in cell cultures of chick embryo, and (3) Rubella Virus Live, the Wistar RA 27/3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) culture. When the lyophilized vaccine is reconstituted as directed, the product contains not less than 1000 $CCID_{50}$ (cell culture infectivity dose) measles virus, 5000 $CCID_{50}$ mumps virus, and 1000 $CCID_{50}$ rubella virus (minimum potencies at expiry, 8 hours post-reconstitution). The product is intended for single-dose administration and contains no preservative. Sterile diluent is provided for reconstitution.

14 Clinical Trials

14.1.Clinical Trials by Indication

The original trivalent measles, mumps and rubella vaccine, M-M-R®, was first licensed in the United States in 1971 and in Canada in 1972. This formulation contained the HPV 77 DE strain of live rubella virus, also used in the monovalent rubella virus vaccine (MERUVAX®). In developing M-M-R® II, the rubella component of M-M-R® (HPV 77 DE) was exchanged with the Wistar RA 27/3 attenuated rubella strain. M-M-R® was subsequently discontinued, and M-M-R® II (Wistar RA 27/3) was licensed in the United States in 1978 and in Canada in 1979. The Wistar RA 27/3 attenuated rubella strain is cultured in human diploid fibroblasts and was developed by Plotkin in 1965. Comparative studies using the 2 rubella vaccine virus strains showed that RA 27/3 induced stronger rubella-specific immune responses, was associated with lower incidence of adverse experiences, and was associated with lower incidence of breakthrough infection after exposure with wild type rubella virus. Since 1978, the Wistar RA 27/3 strain has been used in place of the HPV 77 DE strain and is the only rubella strain used in all rubella containing vaccines licensed by Merck Sharp & Dohme LLC.

From 1975 to 1978, 7 studies involving approximately 2,000 subjects (8 months to 27 years of age), were conducted to support the licensure of M-M-R® II in many parts of the world, including Canada. These studies compared the immunogenicity, safety, and tolerability of different combinations of measles, mumps, and rubella live virus vaccines. A summary of 6 out of the 7 studies is included in Table 5.

The seventh study, Protocol 484, compared the immunogenicity and clinical tolerability of M-M-R® II Lot 621/C D763 or M-M-R®. One hundred fifty-five (155) subjects 13 months to 27 years of age were enrolled. Of the children with available antibody results, seroconversion was observed in 98% (30/31) of those receiving HPV 77 DE containing vaccine and in 100% (47/47) of those receiving RA 27/3 containing vaccine.

The most frequent systemic reactions reported in the original study summaries were upper respiratory illness (32%), gastrointestinal illness (23%), irritability (17%), and anorexia (17%). Measles like rash

occurred in 5% of subjects immunized with trivalent vaccine containing the RA 27/3 rubella strain. Seroconversion rates observed at 6 weeks postvaccination among this triple seronegative population were 95% for measles, 96% for mumps, and 99% for rubella.

Table 5 – Summary of Immunogenicity Results in Children Initially Seronegative to Measles, Mumps, and Rubella Who Received Trivalent Measles, Mumps and Rubella Vaccine Containing the RA 27/3 Rubella Strain

					Antibody Responses among Triple Seronegative Subjects								
					Measles (HI)			Mumps (Neut)			Rubella (Neut)		
Study No.	Lot No.	Range	Mean (Year)	N	Observed Response		GMT	No. Converting/ No. Seronegative		GMT	No. Converting/ No. Seronegative		GMT
442	621	10 m to 7 y	3.7	199	100%	(23/23)	99	96%	(22/23)	7	100%	(23/23)	149
443	621	11 m to 8 y	1.7	105[1]	94%	(65/69)[1]	56	96%	(66/69)[1]	8	100%	(69/69)[1]	133
459	60664	14 m to 4 y	1.5	59	93%	(13/14)	62	93%	(13/14)	17	100%	(14/14)	269
467	621	11 m to 7 y	1.9	137[2]	95%	(55/58)[2]	71	98%	(57/58)[2]	7	100%	(58/58)[2]	146
511	60664	8 m to 11 y	3.3	50	82%	(9/11)	20	91%	(10/11)	5	100%	(11/11)	226
	60665	11 m to 7 y	3.3	50	80%	(4/5)	25	80%	(4/5)	11	100%	(5/5)	169
	60666	11 m to 11 y	4.2	50	100%	(2/2)	28	100%	(2/2)	8	100%	(2/2)	256
513	60664	12 m to 7 y	1.6	58	94%	(30/32)	74	94%	(30/32)	16	100%	(32/32)	250
	60665	12 m to 4 y	1.6	58	97%	(35/36)	72	97%	(35/36)	23	97%	(35/36)	307
	60666	11 m to 4 y	1.5	59	97%	(33/34)	66	97%	(33/34)	27	97%	(33/34)	256
				Totals	95%	(269/284)	63	96%	(272/284)	11	99%	(282/284)	179

HI = Hemagglutination-inhibition.
Neut = Neutralizing.
y = Years.
m = Months.
N = Number vaccinated.
Observed Response = number converted/number initially seronegative.
[1] Three of these subjects were immunized with a 1.0 mL dose of trivalent vaccine containing RA 27/3 strains, 1 subject was triple seronegative prior to immunization and is included in this table.
[2] Twenty subjects were immunized with a 1.0 mL dose of trivalent vaccine containing RA 27/3 strains, 9 subjects were triple seronegative prior to immunization and are included in this table.

Protocol 009 (M-M-R® II [measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.] with rHA replacement study) was designed to (1) demonstrate that the antibody response rates to measles, mumps, and rubella among children who received M-M-R® II manufactured with rHA will be similar to the antibody response rates among children who receive M-M-R® II manufactured with HSA; (2) to demonstrate that M-M-R® II manufactured with rHA will induce acceptable antibody response rates to measles, mumps, and rubella; and (3) to demonstrate that M-M-R® II with rHA will be generally well tolerated. This was a double blind (using in house blinding procedures), randomized, comparative multicenter study of 1282 healthy children at 12 to 18 months of age. Eligible subjects were randomized to receive either an investigational formulation of M-M-R® II manufactured with rHA or currently licensed M-M-R® II manufactured with HSA. In order to determine if any rHA manufacturing residual would elicit an immune reaction, certain adverse experiences of special interest (AESI) that are indicative of hypersensitivity reaction were prespecified in the protocol and prompted for on the Vaccination Report Card (VRC). The incidence of injection site adverse experiences, temperature ≥38.9 °C ([≥102.0 °F], oral equivalent or abnormal), non injection site rashes, other local and systemic adverse experiences were reported for the 42 days (6 weeks) following vaccination. Serum samples were obtained from each subject immediately prior to the vaccination on Day 0, and 6 weeks postvaccination.

The primary endpoints used to assess immunogenicity 6 weeks postvaccination were the antibody response rates for measles, mumps, and rubella, defined as the proportion of subjects who developed

serum antibody levels >120 mIU/mL for measles, >10.0 ELISA antibody units/mL for mumps, or >10.0 IU/mL for rubella. The primary analysis of the response rate to measles, mumps, and rubella were based on a per protocol subject population, which included subjects without protocol violations who had a valid baseline and week 6 titer values for analysis, and whose baseline measles antibody titers were <120 mIU/mL, whose baseline mumps antibody titers were <10.0 ELISA antibody units/mL, and whose baseline rubella antibody titers were <10.0 IU/mL. Both the primary immunogenicity hypotheses of similarity to the control group and for acceptability of antibody responses in recipients of M-M-R® II with rHA were satisfied for measles, mumps, and rubella. The 2 sided 90% confidence intervals on the differences in estimated antibody response rates to measles, mumps, and rubella between recipients of M-M-R® II with rHA and recipients of M-M-R® II with HSA all excluded a decrease of 5 percentage points or more and thus support a conclusion of similarity between the 2 treatment groups for each antigen. The lower bounds of the 2 sided 95% CI for each of the 3 antibody response rates in recipients of M-M-R® II with rHA were all greater than 90%, supporting the conclusion of acceptable antibody response rates. Measles, mumps, and rubella GMTs measured 6 weeks postvaccination were comparable between the two treatment groups. Summaries of the immunogenicity results measured in the 2 treatment groups are provided in tables 6 (non inferiority analysis) and 7 (acceptability analysis).

Table 6 – Statistical Analysis of Similarity of Measles, Mumps, and Rubella Antibody Responses in Initially Seronegative Subjects (Per-Protocol Analysis)

		M-M-R® II With rHA (N=641)		M-M-R® II With HSA (N=638)		Estimated Difference[†‡] (Percentage Points) (90% CI)[‡]	Similarity Conclusion
Antibody (ELISA)	Parameter	n	Estimated Response[†]	n	Estimated Response[†]		
Measles	% ≥120 mIU/mL	531	98.3%	498	98.8%	-0.5% (-1.9%, 0.8%)	Similar[§]
Mumps	% ≥10.0 ELISA antibody units/mL	563	99.4%	533	97.9%	1.5% (0.4%, 2.8%)	Similar[§]
Rubella	% ≥10.0 IU/mL	572	99.6%	543	99.6%	0.0% (-0.8%, 0.8%)	Similar[§]

[†] Responses and their difference were based on a statistical analysis model adjusting for study centers.

[‡] [M-M-R® II with rHA] - [M-M-R® II with HSA].

[§] A lower bound of 90% confidence interval (CI) on the difference excluding a decrease of 5 percentage points or more implies the difference is statistically significantly less than the prespecified clinically relevant decrease of 5 percentage points and allows for a conclusion of similarity (non-inferiority). The associated 1-sided p-value for each test is <0.001 (a p-value ≤0.05 implies that the difference is statistically significantly less than the prespecified difference of 5 percentage points).

N=Number of subjects vaccinated in each treatment group.

n=Number of subjects initially seronegative for measles, mumps, and rubella contributing to the per-protocol analyses.

rHA=Recombinant human albumin.

HSA=Human serum albumin.

ELISA=Enzyme-linked immunosorbent assay.

Table 7 – Statistical Analysis of Acceptability of Measles, Mumps, and Rubella Responses in Initially Seronegative Subjects (Per-Protocol Analysis)

Antibody (ELISA)	Parameter	M-M-R® II With rHA (N=641) n	M-M-R® II With rHA (N=641) Observed Response (95% CI)†	Acceptability Conclusion
Measles	% ≥120 mIU/mL	531	98.3% (96.8%, 99.2%)	Acceptable†
Mumps	% ≥10.0 ELISA antibody units/mL	563	99.5% (98.5%, 99.9%)	Acceptable†
Rubella	% ≥10 IU/mL	572	99.7% (98.7%, 100%)	Acceptable†

† The lower bound of the 95% confidence interval (CI) being >90% implies that the value of the parameter is statistically significantly greater than the prespecified acceptability criterion (90%) and allows for a conclusion of acceptability.

N=Number of subjects vaccinated in treatment group.

n=Number of subjects initially seronegative for measles, mumps, and rubella contributing to the per-protocol analyses.

rHA=Recombinant human albumin.

ELISA=Enzyme-linked immunosorbent assay.

For safety evaluation, one or more adverse experiences occurred in 520 (82.0%) recipients of

M-M-R® II with rHA and in 506 (80.1%) recipients of M-M-R® II with HSA. One or more vaccine-related adverse experiences occurred in 308 (48.6%) recipients of M-M-R® II with rHA and in 276 (43.7%) recipients of M-M-R® II with HSA. Two-hundred twenty-six (35.6%) recipients of M-M-R® II with rHA compared with 187 (29.6%) recipients of M-M-R® II with HSA reported injection-site adverse experiences that were vaccine related. Vaccine related systemic adverse experiences were reported for 139 (21.9%) recipients of M-M-R® II with rHA compared to 149 (23.6%) recipients of M-M-R® II with HSA. Only 8 subjects (3 recipients of M-M-R® II with rHA and 5 recipients of M-M-R® II with HSA) experienced a serious adverse experience during the safety follow up period. None of these 8 serious adverse experiences was determined by the investigator to be vaccine related (see 8 Adverse Reactions). No subjects died during the study and no subjects were discontinued from the study due to an adverse experience.

The two treatment groups were generally comparable in terms of the incidence rates of adverse experiences, although a significantly higher proportion of subjects who received M-M-R® II with rHA reported an injection site adverse experience compared with those who received M-M-R® II with HSA. The incidence rates of these local reactions were found to be within the historical ranges observed in previous M-M-R® II studies and are thought to be related to variability between lots. Moreover, incidence rates of potential hypersensitivity reactions (AESI) were well balanced between the 2 treatment groups and no subjects in either treatment group had detectable antibody to albumin at baseline or 6 weeks postvaccination.

Overall, the study supports the replacement of HSA with rHA in the manufacturing of viral bulks for M-M-R® II based on the following similar seroconversion rates for measles, mumps, and rubella induced by M-M-R® II manufactured with rHA compared with M-M-R® II manufactured with HSA. M-M-R® II with rHA is generally well tolerated and has safety and tolerability profiles comparable to those of M-M-R® II with HSA, the currently licensed vaccine.

In an open label clinical trial 752 children 12 through 18 months of age received M-M-R® II either intramuscularly (n=374) or subcutaneously (n=378), concomitantly with VARIVAX. Antibody responses to measles, mumps, and rubella viruses were measured by ELISAs using sera obtained 6 weeks

postvaccination. For anti-measles virus, anti-mumps virus and anti-rubella virus, seroresponse rates were defined as the percentage of children seronegative at baseline who achieved antibody titers above the respective seroresponse threshold for each assay 6 weeks post vaccination. Seroresponse thresholds were defined as 255 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles virus, anti-mumps virus, and anti-rubella virus antibodies, respectively. For each vaccine antigen at least 89% of enrolled children were seronegative at baseline. In a prespecified primary analysis, seroresponse rates to measles, mumps and rubella viruses were noninferior for the intramuscular group compared to the subcutaneous group (the lower bound of the 95% confidence interval for the difference in seroresponse rates [intramuscular group minus subcutaneous group] was > -10%).

The proportions of children achieving antibody titers above the seroresponse thresholds for measles, mumps, and rubella viruses were as follows: 94.3%, 97.7%, and 98.1%, respectively, in the intramuscular group and 96.1%, 98.1%, and 98.1%, respectively, in the subcutaneous group.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

Carcinogenicity: M-M-R® II has not been evaluated for its carcinogenic potential.

Genotoxicity: M-M-R® II has not been evaluated for its genotoxicity potential.

Reproductive and Developmental Toxicology: M-M-R® II has not been evaluated for its potential to impair fertility. It is also not known whether M-M-R® II can cause harm to the fetus when administered to a pregnant woman (see 7 Warnings And Precautions, 7.1.1 Pregnancy).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

M-M-R® II

(measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.)

This Patient Medication Information is written for the person who will be taking **M-M-R® II**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **M-M-R® II**, talk to a healthcare professional.

What M-M-R® II is used for:

M-M-R® II is an injectable live virus vaccine to help prevent measles , mumps, and rubella .

How M-M-R® II works:

Your doctor has recommended or administered M-M-R® II to help protect you or your child against measles, mumps, and rubella. The vaccine can be administered to persons 12 months of age or older.

- Measles is a serious disease that is very easily passed from one person to another. It causes a high fever, cough, and a rash and lasts for 1 to 2 weeks. One out of every 10 children who catch measles will also have an ear infection or pneumonia. On rare occasions, measles can also cause an infection of the brain that could lead to seizures, hearing loss, mental retardation, and even death. Babies and adults who catch measles are often much sicker for a longer time or are more likely to die than elementary school children and teenagers who catch measles.
- Mumps is easily passed from one person to another and causes fever, headache, and swollen, painful glands under the jaw (salivary glands). It can sometimes be a very serious disease and usually lasts for several days. Mumps can cause a mild inflammation of the coverings of the brain and spinal cord (meningitis) in about 1 person in every 10 who catch it. About 1 out of every 4 teenage or adult males with mumps will have a painful swelling of the testicles for several days (this does not usually affect their ability to father children). Teenagers and adults, especially males, who catch mumps are often much sicker and more likely to suffer longer than children do.
- Rubella is usually a mild disease that causes a mild fever, swollen glands in the neck, pain and swelling in the joints, and a rash that lasts for a short time but is very dangerous if a pregnant woman catches it. Women who catch rubella when they are pregnant can have babies who are stillborn, or have heart disease, blindness, deafness, or problems with learning.

The ingredients in M-M-R® II are:

Medicinal ingredient: The medicinal ingredient is an injectable live attenuated virus vaccine to help prevent measles, mumps and rubella virus.

Non-medicinal ingredients: M-M-R® II contains neomycin, gelatin and recombinant human albumin as

inactive ingredients. Tell your doctor if you or your child has ever had an allergic reaction to these ingredients.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

M-M-R® II comes in the following dosage forms:

- a box of 10 single-dose vials of lyophilized vaccine, and
- a box of 10 vials (0.7 mL) of sterile diluent.

Do not use M-M-R® II if the recipient:

- is allergic to any of its components (including neomycin)
- is pregnant (in addition, pregnancy should be avoided for 1 month after vaccination)
- has a fever
- has active untreated tuberculosis
- is taking medications to suppress their immune system (other than corticosteroid replacement)
- has a blood disorder or any type of cancer that affects their immune system
- has an immune deficiency as a result of a disease or a treatment

To help avoid side effects and ensure proper use, talk to your healthcare professional before your child gets M-M-R® II. Talk about any health conditions or problems you or your child may have, including if:

- you or your child has or has had any medical problems, and about any allergies (especially to neomycin).
- you or your child has a history of convulsions or a brain injury, or a low blood platelet count.

Use in children

M-M-R® II should be used in children 12 months of age or older. However, your doctor may recommend that M-M-R® II be given to infants who are less than 12 months of age in special situations.

Use in pregnancy

M-M-R® II should not be administered to pregnant women. Women of child-bearing age should take the necessary precautions to avoid pregnancy for 1 month following vaccination.

Use in breastfeeding

Tell your doctor if you are breastfeeding or intend to breastfeed. Your doctor will decide if you should receive M-M-R® II**.**

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with M-M-R® II:

- Administration of immunoglobulins with M-M-R® II may interfere with immune response.

- Tell your doctor if your child has received blood or plasma transfusions or administration of human serum globulin within the last 3 months.

How to take M-M-R® II:

M-M-R® II will be given to your child by a healthcare professional in a healthcare setting.

Usual dose:

- M-M-R® II is given to persons 12 months of age or older. The dose of the vaccine is the same for everyone.
- For persons vaccinated at 12 months of age or older, a second dose of the vaccine is recommended at a later date which will be decided by your doctor.
- Children first vaccinated at less than 12 months of age should receive two additional doses after reaching 12 months of age.
- Non-pregnant adolescent and adult females of childbearing age who are susceptible to rubella can be vaccinated with M-M-R® II (or live attenuated rubella virus vaccine) if certain precautions are observed (see Use in Pregnancy). It has been found convenient in many instances to vaccinate women who are susceptible to rubella in the immediate post-partum period.

See your doctor for more details.

Overdose:

If you think you, or a person you are caring for, have taken too much M-M-R® II, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

Your doctor will decide when to give the missed dose.

Possible side effects from using M-M-R® II?

These are not all the possible side effects you may have when taking M-M-R® II. If you experience any side effects not listed here, tell your healthcare professional.

Any vaccine may have unintended or undesirable effects, so-called side effects. The most common is burning and/or stinging at the injection site for a short time. Transient joint pain and/or swelling have occurred more frequently in adult females; sometimes these symptoms may be chronic. Occasionally, fever and rash may occur. Rarely, unusual bleeding or bruising under the skin, and swelling of the testicles may occur.

Other side effects may also occur rarely and some of these may be serious. These include allergic reactions, seizures, and inflammation of the nervous system (brain and/or spinal cord).

Your doctor has a more complete list of side effects.

Tell your doctor promptly about any of these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Merck Canada Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

Storage:

Vial of powder: Store at 2°C to 8°C. The vaccine may also be stored in a freezer at temperatures above -50°C; if subsequently transferred to a refrigerator, the vaccine may be placed back in the freezer. Keep the vial in the outer carton in order to protect from light.

Diluent: The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. Refrigeration of the diluent is not needed. Store at 2°C to 27°C.

All vaccines must be discarded after the expiration date.

Keep out of reach and sight of children.

If you want more information about M-M-R® II:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.merck.ca, or by calling 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

Date of Authorization: 2025-10-16