Public Assessment Report

M-M-R® II

INFORMASI PRODUK

Nama obat	:	M-M-R II
Bentuk sediaan	:	Serbuk injeksi
Zat aktif	:	Tiap dosis mengandung : - Live attenuated measels virus (Edmonston strain) tidak kurang dari 1000 $CCID_{50}$ - Live attenuated mumps virus (Jeryl Lynn™ strain) tidak kurang dari 12500 $CCID_{50}$ - Live attenuated rubella virus (Wistar RA27/3 strain) tidak kurang dari 1000 $CCID_{50}$
Kemasan	:	Dus, 1 vial @ 0,5 ml + 1 vial pelarut @ 0,7 mL
Pendaftar	:	PT Organon Pharma Indonesia Tbk
Produsen	:	Diproduksi Oleh Merck Sharp & Dohme Corp., Durham, United States Of America Dirilis Oleh Merck Sharp & Dohme BV, Haarlem, Netherlands
Kategori Registrasi	:	Registrasi produk biologi yang sudah terdaftar dengan indikasi dan posologi baru
Indikasi yang diajukan	:	***INDICATIONS*** *M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older (see DOSAGE AND ADMINISTRATION).* *There is some evidence to suggest that infants who are born to mothers who had wild type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.* *Infants who are less than 12 months of age may fail to respond to the measles component of the vaccine due to presence in the circulation of residual measles antibody of maternal origin; the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which wild-type measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching 12 to 15 months of age.*
Posologi yang diajukan	:	***DOSAGE AND ADMINISTRATION*** *FOR SUBCUTANEOUS ADMINISTRATION* *Do not inject intravascularly* *Do not give immune globulin (IG) concurrently with M-M-R II. (See DRUG INTERACTIONS.)* *The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.* *CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.* *To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.*

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-M-R II, when reconstituted, is clear yellow.

RECOMMENDED VACCINATION SCHEDULE
Individuals first vaccinated at 12 months of age or older should be revaccinated at 4 to 6 years of age since increased risk of exposure typically occurs around elementary school entry.Revaccination is intended to seroconvert those who do not respond to the first dose.

MEASLES OUTBREAK SCHEDULE
Infants Between 6 to 12 Months of Age
Local health authorities may recommend measles vaccination of infants between 6 to 12 months of age in outbreak situations. This population may fail to respond to the components of the vaccine. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established. The younger the infant, the lower the likelihood of seroconversion. Such infants should receive a second dose of M-M-R II at 12 to 15 months of age followed by revaccination at 4 to 6 years of age.

MUMPS OUTBREAK SCHEDULE
Local health authorities may recommend mumps vaccination in a mumps outbreak situation

PENGANTAR

M-M-R- II merupakan vaksin yang mengandung antigen measles, mumps, dan rubella yang diproduksi oleh MSD Corp., Carolina Utara Amerika Serikat dikemas dan dirilis oleh MSD BV Harleem, Belanda. Vaksin ini telah disetujui untuk usia 15 bulan ke atas. Saat ini mengajukan perubahan indikasi dari 15 bulan ke 12 bulan dan perubahan posologi dengan dokumen pendukung seperti yang dijelaskan di aspek khasiat dan keamanan.

ASPEK MUTU

N/A

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik
N/A

Studi Klinik

1. Perubahan usia dari 15 bulan menjadi 12 bulan. Perubahan ini didukung oleh :
   a. SPC ProQuad (M-M-R II + Varivax produksi MSD) dimana usia yang disetujui mulai 12 bulan.
   b. Studi terpublikasi Wiedmann, Richard T el al. 2015. Studi ini bertujuan untuk membandingkan imunogenisitas dan keamanan antara M-M-R II yang diproduksi menggunakan *human serum albumin* dan M-M-R II yang diproduksi menggunakan *recombinant serum albumin*. Studi ini merupakan studi double blind, random 1: 1. Dilakukan pada anak sehat usia12-18 bulan dan 3-4 tahun. Studi menilai keamanan (AE, termasuk hipersensitivitas) dan imunogenisitas (titer antibodi, serokonversi). Studi menunjukkan pemberian M-M-R II rHA dan M-M-R II HSA menghasilkan imunogenisitas yang cukup baik terlihat dari persentase subjek GMT diatas cut off (measles, mumps, rubella masing masing 97,0% vs 97,2% ; 99,5% vs 97,9% ; 99,7% vs 99,6%) dan nilai GMT (1636,1 vs 1520,8 ; 98,2 vs 85,8 ; 113,0 vs 106,4). Profil keamanan dapat ditoleransi.

2. Penambahan klim pada indikasi “There is some evidence to suggest that infants who are born to mothers

who had wild-type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization." Data penunjang:

a. Linneman, C.C., et al: *Measles Immunity After Vaccination: Results in Children Vaccinated Before 10 Months of Age, Pediatrics, 69(3): 332-335, March 1982.* Imunitas terhadap measles dinilai pada sebuah studi yang melibatkan 72 anak, yang menerima dosis pertama pada < 10 bulan dan dosis kedua > 1 tahun. 29 (40%) dari subjek tidak terdeteksi antibodinya. Diantara subjek dengan titer antibody yang rendah, 15 diberikan dosis ketiga vaksin measles, namun 5 orang diantaranya tetap tidak merespon. Studi ini menuinjukkan revaksinasi tidak bermanfaat bila subjek mendapatkan vaksin measles pertama di usia < 12 bulan.
b. Stetler, H.C., et al: *Impact of Revaccinating Children Who Initially Received Measles Vaccine Before 10 Months of Age, Pediatrics 77(4): 471-476, April 1986. Impact of Revaccinating Children Who initially Received Measles Vaccine Before 10 Months of Age.* 254 bayi menerima vaksin measles pada usia < 10 bulan dan mendapat vaksinasi ulang saat usianya ≥ 15 bulan. Respon imun 254 bayi ini dibandingkan dengan 129 bayi yang menerima dosis pertama saat usianya ≥ 15 bulan. Sampel darah diambil setelah revaksinasi (kelompok uji) dan vaksinasi primer (kelompok kontrol), 3 minggu dan 8 bulan kemudian. Hasilnya, 3 minggu setelah revaksinasi / vaksinasi primer, subjek dengan IgM terdeteksi lebih banyak di kelompok kontrol (yang menerima vaksinasi pertama saat usia ≥ 15 bulan) yaitu 74% vs 22,2%. Setelah 8 bulan untuk parameter HI dan ELISA juga lebih tinggi di kelompok kontrol.

3. Perubahan klim revaksinasi pada usia 4-6 tahun tidak disertai studi klinik untuk membuktikan efikasi dan keamanannya.

4. Perubahan klim terkait jadwal vaksinasi saat outbreak.

    a. Klaim ini memberikan informasi tentang rekomendasi vaksin measles (monovalent) bisa diberikan pada usia 6 – 12 bulan pada keadaan outbreak. Untuk bayi-bayi yang telah menerima vaksin measles di usia kurang dari 12 bulan, vaksin M-M-R II tetap direkomendasikan di usia 12-15 bulan yang diikuti dengan revaksinasi di usia 4 – 6 tahun.
    b. Data imunogenisitas penggunaan vaksin measles (monovalent) pada usia 6 bulan terdapat pada jurnal Johnson, Candice E. 1994. Measles Vaccine Immunogenicity in 6- Versus 15- Month-Old Infants Born to Mothers in the Measles Vaccine Era. Jurnal ini sebagai dokumen penunjang untuk klaim "Local health authorities may recommend measles vaccination of infants between 6 to 12 months of age in outbreak situations".
    c. Data penunjang untuk penggunaan M-M-R II di usia 12-15 bulan untuk bayi yang telah menerima vaksin measles kurang dari 12 bulan terdapat pada jurnal Stetler C, Harrison, et al. 1986. Impact of Revaccinating Children Who Initially Received Measles Vaccine Before 10 Months of Age.

Hasil evaluasi terhadap studi di atas sebagai berikut:

1. Untuk perluasan indikasi mulai usia 12 bulan.
    a. Studi P009 yang menunjukkan pemberian M-M-R II Recombinant Serum Albumin dan M-M-R II Human Serum Albumin pada anak usia11-19 bulan menghasilkan imunogenisitas yang baik terlihat dari persentase subjek GMT diatas cut off (measles, mumps, rubella masing masing 97,0% vs 97,2% ; 99,5% vs 97,9% ; 99,7% vs 99,6%) dan nilai GMT (1636,1 vs 1520,8 ; 98,2 vs 85,8 ; 113,0 vs 106,4) dengan profil keamanan dapat ditoleransi.
    b. Produk ProQuad yang mengandung komponen M-M-R II (M-M-R II + Varivax) sudah disetujui mulai usia 12 bulan.

2. Untuk penambahan klim pada indikasi "*There is some evidence to suggest that infants who are born to mothers who had wild-type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization*" didukung :
    a. Linneman, 1982 yang menunjukkan revaksinasi tidak bermanfaat bila subjek mendapatkan vaksin measles pertama di usia < 12 bulan.
    b. Stetler, 1986 yang menunjukkan subjek dengan IgM terdeteksi lebih banyak di kelompok kontrol

yang menerima vaksinasi pertama saat usia >=15 bulan dibanding kelompok uji yang menerima vaksin < 10 bulan (74% vs 22,2%).

3. Perubahan klim revaksinasi pada usia 4-6 tahun tidak disertai studi klinik untuk membuktikan efikasi dan keamanannya.

4. Perubahan klim terkait jadwal vaksinasi saat outbreak measles dan mumps pada bayi usia <12 bulan:
   a. Berdasarkan artikel Johnson, Candice E. 1994, dengan vaksin yang digunakan pada usia anak 6-12 bulan adalah Attenuax dan tidak dijelaskan apakah vaksin diberika saat outbreak, menunjukkan subjek seropositif measles yang lebih rendah dibandingkan yang menerima pada usia 15 bulan (74% vs 100%).
   b. Berdasarkan artikel Stetler C, Harrison, et al. 1986, menunjukkan persentasi subjek seropositif measles pada anak < 10 bulan setelah revaksinasi pada usia 15 bulan sebanding dengan subjek penerima vaksinasi primer pada usia 15 bulan, pada saat outbreak (95,9% vs 99,2%). Namun tidak diketahui persentase subjek seropositive setelah pemberian vaksin pertama pada usia < 10 bulan tersebut.
   c. Tidak ada data terkait respon antibodi mumps dan rubella.

KEPUTUSAN
Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi perubahan indikasi dan posologi M-M-R II serbuk injeksi dapat **diterima dengan revisi** sebagai berikut:

INDICATIONS
M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older (see DOSAGE AND ADMINISTRATION).

There is some evidence to suggest that infants who are born to mothers who had wild type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.

Infants who are less than 12 months of age may fail to respond to the measles component of the vaccine due to presence in the circulation of residual measles antibody of maternal origin; the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which wild-type measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching 12 to 15 months of age.

DOSAGE AND ADMINISTRATION
FOR SUBCUTANEOUS ADMINISTRATION
Do not inject intravascularly

Do not give immune globulin (IG) concurrently with M-M-R II. (See DRUG INTERACTIONS.)

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

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