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DEEL IA - ADMINISTRATIEVE GEGEVENS

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Plaats: HAARLEM

Datum: 2 december 1993

Manager Pharmaceutical Registration
(Functie en handtekening (en) van de aanvrager)

Deze aanvraag betreft:

■ Een nationale aanvraag (nummer (indien beschikbaar):
o Een EG-aanvraag overeenkomstig Richtlijn 83/570/EEG (meerlanden-procedure) rapporteur:
o Een EG-aanvraag overeenkomstig Richtlijn 87/22/EEG (overleg-procedure) rapporteur:
  o Lijst A
  o Lijst B
    datum van goedkeuring als produkt van lijst B door CPMP

o Een aanvraag waarbij wordt verwezen naar een eerdere aanvraag: (produkt, nummer vergunning)

o Overlegprocedure met betrekking tot een wijziging: Nummer advies van de overlegprocedure waarop deze aanvraag betrekking heeft/nationale nummer aanvraag:

o Een opnieuw ingediende aanvraag (nummer voorheen ingediende nationale aanvraag)

. . . . . .

o Een geneesmiddel met een nieuwe werkzame stof
o Een geneesmiddel met een nieuwe combinatie van bekende werkzame stoffen
o Een geneesmiddel met een nieuwe indicatie
o Een andere aanvraag (geef omschrijving, bijvoorbeeld een nieuwe farmaceutische vorm of een nieuwe sterkte)

. . . . . .

o Een vereenvoudigde aanvraag
o o overeenkomstig Richtlijn 65/65, artikel 4, punt 8a) i)
(schriftelijke toestemming van de houder van de vergunning voor het oorspron- kelijke geneesmiddel meezenden)
o overeenkomstig Richtlijn 65/65, artikel 4, punt 8a) ii)
o overeenkomstig Richtlijn 65/65, artikel 4, punt 8a) iii)
(er dient te worden aangetoond dat een in wezen gelijkwaardig produkt minstens zestien jaar volgens de geldende communautaire bepalingen in de Gemeenschap is toegelaten en in de lidstaat waarvoor de aanvraag wordt ingediend, in de handel wordt gebracht)
o "hybride" aanvragen (overeenkomstig III/3879/90):
  o ander zout/ester/derivaat
  o ander therapeutisch gebruik
  o andere toedieningsvorm
  o ander doseringsregime
  o andere sterkte
  o produkten met hogere biologische beschikbaarheid
  o overige

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1. Voorgestelde naam van het geneesmiddel in de betrokken Lidstaat:

Indien bij een communautaire procedure verschillende namen in verschillende lidstaten worden voorgesteld, moeten deze worden vermeld:

Land: Nederland Naam: M-M-R II

[redacted] D

Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of human immune serum globulin. Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7-28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.

There are no reports of transmission of the live measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R®II. Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine; no studies have been reported to date of the effect of live measles virus vaccines on untreated tuberculous children. As for any vaccine, vaccination with M-M-R®II may not result in seroconversion in 100% of susceptible persons given the vaccine.

Pregnancy

Animal reproduction studies have not been conducted with M-M-R®II. It is also not known whether M-M-R®II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination.

Nursing mothers.

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating post-partum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. Caution should be exercised when M-M-R®II is administered to a nursing woman.

e) Marketing/post-marketing

M-M-R®II was first licensed in the United States of America on September 15, 1978, and is now licensed in more than 30 countries, worldwide. During the period 1978 to 1992, over [redacted] doses of this vaccine have been supplied worldwide.

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M-M-R® II

2. CLINICAL EXPERT OPINION – TABLE OF CONTENTS

5.g. Vaccination and Pregnancy

Since the RA 27/3 strain was approved in the United States in 1974, there have been 635 reported cases in which women were vaccinated with the RA 27/3 strain in the three months preceding pregnancy or in the weeks following conception. The baby's condition at birth was documented; none of the 522 live births had any abnormalities compatible with congenital rubella syndrome; 20 cases ended in abortion or premature birth; 54 therapeutic abortions were reported; and 42 cases were not documented [Table 14] [28]. The risk of congenital rubella syndrome over the duration of this study was 0%, in comparison to a risk of 20% in a non immunized population having rubella during the first trimester of pregnancy.

5.h. Protective Efficacy of M-M-R® II Vaccine

The protective efficacy of the vaccine must be judged essentially on the protection it induces against the disease in consideration. It can be assessed by the measure of incidence of this disease on a national level as a result of requirement of reporting of new cases with the health authorities. The protection can also be estimated by the measure of its effectiveness during an epidemic.

Measles

In the United States, the incidence of measles has diminished by 99.8% from 1950-1962 (the period preceding the introduction of the first measles vaccine) to 1983. During this time the number of cases reported annually declined from 315 per 100,000 persons to 0.6 per 100,000 persons [2]. The number of related deaths and cases of acute encephalitis have similarly declined [2]. The number of cases of subacute sclerosing panencephalitis gradually declined almost to zero beginning several years later [2]. The vaccine effectiveness observed during an epidemic remained high in children vaccinated at the age of 15 months or older [29].

During the period 1963-1982, 18.9 million doses of vaccine containing Edmonston B strain and 117.7 million doses of vaccine containing the more attenuated measles virus (ATTENUVAX®) were distributed in the United States Note that ATTENUVAX® has been the only monovalent measles vaccine available in the United States since 1976.

In Sweden, a double vaccination schedule with M-M-R® II (first dose at 18 months, booster at age 12) was introduced in 1982. The annual incidence of measles fell accordingly from 76 cases per 100,000 persons in 1982 to 1.2 cases per 100,000 in 1988 [30]. This decrease must be attributed to the M-M-R® II vaccine (known as VIRIVAC® in Sweden), as it has been the only anti-measles, mumps, rubella vaccine available there since 1982.

In Finland, a double vaccination with the M-M-R® II vaccine permitted a 93% decrease in the number of measles cases between 1982 and 1985 [31]. In this country as well, the only anti-measles, mumps, rubella vaccine is the M-M-R® II vaccine.

TABLE 14

Pregnancy outcomes for 635 recipients of RA 27/3 vaccine — United States, January 1979-December 1986

Prevaccination Immunity Status	Total Women	Live Births	Spontaneous Abortions and Stillbirths	Induced Abortions	Outcome Unknown
Susceptible	224	172 *	11	30	13
Immune	32	30	1	0	1
Unknown	379	320 †	8	24	28
Total	635	522	20	54	42

*Includes two twin births.
†Includes one twin birth.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES / PUBLIC HEALTH SERVICE

From MMWR, 457-461, July 24, 1987. [28]