Extension Directives 89/342 and 89/381 EEC

M-M-R®II

Measles, Mumps and Rubella Vaccine, Live, MSD

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Expert Report on the

Clinical Documentation

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M-M-R® II

2. CLINICAL EXPERT OPINION – TABLE OF CONTENTS

6. M-M-R® II Trivalent Measles, Mumps, Rubella Vaccine: Tolerability Study

The analysis of tolerability was based on adverse reactions:

- observed during clinical studies conducted before introduction to the market,
- and made known to Merck & Co., after introduction of the vaccine to the market.

6.a. Adverse Reactions Occurring During Studies Conducted Before Market Production

The tolerability of the M-M-R® II vaccine was studied in the course of 7 clinical studies conducted before placing it on the market. Adverse reactions occurring in the 42 days following vaccination during Studies 511 and 513 conducted with three different lots of vaccines in 325 children are summarized below:

Results

Occurrence of Post-Vaccination Febrile Reaction

Less than half of the vaccinated children had a temperature >37.2°C during the observation period. The occurrence of febrile reaction was not affected by the presence nor the absence of specific antibodies at the time of vaccination, nor by the lot of vaccine utilized. The number of children having a temperature >37.2°C reaches its maximum between the 5th and 12th days following the vaccination as is expected with the monovalent live measles vaccine.

Occurrence of Local and General Symptoms

Local reactions are occurring in 7.3% of cases and are chiefly transient and mild. The general adverse reactions reported most frequently are irritability (2%-23.1% according to the lot of vaccine and the time period includes upper respiratory tract infection (9.1% to 34.5%) or gastroenteritis (3% to 30.3%). Morbilliform-type rashes occur in 1.8%-11.4% of patients between the 5th and 12th day after vaccination.

The vaccine is generally well-tolerated; the adverse reactions expected between the 5th and 12th day are infrequent and well-tolerated. In addition, the cases of upper respiratory tract infection and gastroenteritis may also have been provoked by intercurrent bacterial or viral infections which occur frequently at that age. The long period of observation (42 days) no doubt increased this phenomenon.

6.b. Adverse Reactions occurring after introduction to the market

In August 1992, an internal analysis was conducted on the worldwide rates of spontaneous adverse experience reporting to Merck & Co., since first introduction of the trivalent vaccine, M-M-R® II on to the market in 1978. The result of this review is given in Part IV, Book 2.

Approximately [redacted] doses of M-M-R® II vaccine have been sold in the domestic and international markets as of August 31, 1992. It is estimated that about [redacted] doses have been administered.

The conclusions from this analysis are:

An evaluation of adverse experiences reported to Merck & Co., Inc. indicates that M-M-R® II is generally well tolerated with few serious vaccine-related adverse experiences reported, considering the vast number of doses sold.

Only six adverse events had spontaneous, voluntary reporting rates of greater than one case per million doses administered. These adverse events include rash (4.32), fever (3.95), systemic reaction (1.28) and febrile convulsions (1.03). Misuse (3.95) and lack of response (3.13) were also reported at a rate greater than one case per million doses distributed.

The total crude rate of reported occurrence of encephalitis and meningitis and meningitis adverse events report after M-M-R® II is 1.1 per million doses administered. This reporting rate includes reported cases and possible cases based on a review of reported selective neurologic adverse events.

The rate of reported deaths is 0.3 per million doses administered. The four most common causes of death were encephalitis (8), unknown cause (8), Sudden Infant Death Syndrome (5), bacterial infection (4).

Abstracts from all publications received during the reporting period are provided as an Annotated Bibliography for M-M-R® II in Part IV, Book 3.

7. Countries in Which the M-M-R® II Vaccine is Marketed (*)

M-M-R® II vaccine is authorized for marketing in over 30 countries (including 11 members of the European Community) and is marketed under name M-M-R® II or under another commercial name.

(*) Please see page 16