Aventis Pasteur MSD

Vaccines for Life

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Brussel, 3 april 2000
SUR/MMR99

Aangetekend

Geachte Hee[redacted]

Betreft : Worldwide safety update report - MMR-Vax® (Mazelen-Bof-Rubella Vaccin)

In bijlage vindt U het 'Safety report' betreffende MMR-Vax® voor de periode van 01 januari 1999 tot 31 december 1999.

Wij wensen U goede ontvangst van bijlage en verblijven, steeds tot uw dienst voor verdere informatie,

[redacted]

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CONFIDENTIAL

MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, (MSD)

SAFETY SUPPLEMENT

01-JAN-1999 to 31-DEC-1999

Worldwide Product Safety & Epidemiology

Merck Research Laboratories

U.S.A.

[redacted]

Description of the data presented

This Periodic Safety Update contains reports that were received by Merck & Co., Inc., from worldwide sources between 01-Jan-1999 to 31-Dec-1999, and entered in the Company's Worldwide Adverse Experience System (WAES) database. In keeping with the ICH E2C guidelines, these reports are referred to as ADRs (adverse drug reactions) throughout this report. The use of the term ADR in this document does not imply that the reported events occurred due to an effect of the vaccine in question, either in the opinion of the Company, or in the opinion of the reporter, or in fact.

Individual patients identified in the literature, where the focus of the article or abstract was a report of an ADR to a Merck product, have been included. References for these published case histories are included in Appendix 7.

The data described in this document include reports in which measles, mumps and rubella virus vaccine was considered the primary suspect therapy in the reported ADR. In the event that the report describes a patient who was taking more than one Merck product, it will be included in this safety update report only if measles, mumps and rubella virus vaccine was considered the primary suspect therapy.

This document only reflects data for measles, mumps and rubella virus vaccine as sponsored by Merck & Co., Inc. and not that of other sponsors of measles, mumps and rubella virus vaccine. However, if it was not possible to identify the sponsor then the sponsor was assumed to be Merck & Co., Inc.

The ADR terminology used in this report reflects the diagnosis or terminology used by the reporter. The reporter terminology is mapped to a Preferred Term using a company-developed dictionary and an autoencoder. Due to evolving dictionary changes and coding guidelines, it is possible that, over time, different Preferred Terms may have been used to identify synonymous reactions. On 20-Oct-97, a new database was implemented and, therefore, the summary tabulations supplied in this report cannot be compared with those in prior reports. Also, some ADR terms that were used in prior PSURs do not appear in the line listings or summary tabulations in this report. The reason that these terms sometimes appear is because, prior to 20-Oct-97, before the new database was implemented, these terms (death, overdose, drug abuse, misuse, and use during pregnancy) were used as ADR terms. The following changes should be noted:

- Death no longer appears as an ADR term when death is an outcome of a reported ADR. If an ADR resulted in death, then this will be noted in the line listing under recovery status. If death is the only reported term, then the term "unknown cause of death" appears in the line listings and summary tabulations.

- Reports identified as overdose without any other reported ADRs may not be included in the line listings or summary tabulations in this safety update report.

- Reports of use during pregnancy without an ADR or without an adverse pregnancy outcome may not be included in the line listings or summary tabulations in this safety update report.

- Reports of drug abuse or product misuse without an ADR may not be included in the line listings or summary tabulations in this safety update report.

For purposes of this report, a serious reaction is defined as one that: results in death, or is life-threatening, or results in a persistent or significant disability/incapacity, or results in or prolongs hospitalization, or is a congenital anomaly, or is a cancer, or is the result of an overdose (accidental or intentional). Since 01-Apr-98, a serious report could also include any report with an "important medical event" (i.e. required medical or surgical intervention to prevent one of the aforementioned outcomes).

Spontaneous reports

Reports on marketed products that were reported spontaneously are presented separately from study reports. Per the general principles of ICH E2C, all adverse experiences from spontaneous reports are assumed to be ADRs unless indicated otherwise by the reporting health care provider. Spontaneous reports also include reports from the literature and from government agencies. Only those reports where a health care provider was identified as a reporting source are included in the line listings and summary tabulations in Appendixes 1, 2, and 3. These reports may have been reported by health care providers, or they may have initially been reported by consumers and follow-up was received from health care providers. Spontaneous reports, where the only information provided was from consumers, are attached as an addendum.

The line listings that describe spontaneous reports where a health care provider has been identified are listed in the body system of the most important ADR term as determined by a Company reviewer and are separated as follows:

Appendix 1, Table 1 - Line listing of reports that have at least one serious ADR term

Appendix 1, Table 2 - Line listing of reports that have only non-serious ADR terms including one that is unlisted

Reports that have only non-serious, listed ADRs do not appear in the line listings.

The period summary tabulations for spontaneous reports are organized by ADR term and categorized by body system. The tabulations are separated as follows:

Appendix 2, Table 1 - Period summary tabulation of ADR terms that are unlisted with the number of serious and non-serious reactions for each term

Appendix 2, Table 2 - Period summary tabulation of ADR terms that are listed with the number of serious and non-serious reactions for each term

In addition, a cumulative summary tabulation (Appendix 3) is provided and includes ADR terms that are serious and unlisted

It is important to emphasize that the spontaneous reporting system is a voluntary system of reporting. Therefore, despite attempts to obtain follow-up information per Standard Operating Procedures, the data are not necessarily complete and may include reports with unsubstantiated diagnoses and incomplete information, irrespective of whether the reports originated from a health care provider or consumer.

Study reports

Study reports include cases from Merck-sponsored investigational clinical trials, from postmarketing clinical trials, compassionate use programs, and from postmarketing surveillance (PMS) studies conducted anywhere in the world. Cases from retrospective and prospective studies that are described in the literature are classified as PMS studies.

The line listing that describes study reports (Appendix 4) include any report that had at least one serious and vaccine-related ADR term. Reports are also included if the vaccine relationships were unknown or not provided. Vaccine relationships are those provided by the reporting investigators.

The period summary tabulations for study reports are organized by ADR term and categorized by body system. The tabulations are separated as follows:

Appendix 5, Table 1 - Period summary tabulation of ADR terms that are serious, unlisted and vaccine related with the number of reactions for each term

Appendix 5, Table 2 - Period summary tabulation of ADR terms that are serious, listed and vaccine related with the number reactions for each term

In addition, a cumulative summary tabulation (Appendix 6) is provided and includes ADR terms that are serious, unlisted and vaccine related.

Description of data tables

The line listings of reports from spontaneous notifications, from studies or compassionate use, from literature, and from regulatory authorities are in body system order. A report that contains more than one ADR term is assigned to the primary body system, i.e. the body system of the most clinically significant ADR term as determined by a Company reviewer. Other ADR terms in the report are listed with it. The listings include the following information:

-the Merck identification number of the report (WAES NO)

-the primary reporting source (SOURCE)

- -Physician
- -Other health care provider
- -Pharmacist
- -Consumer
- -Lawyer
- -Company representative
- -Agency
- -Other

-the country from which the report originated (COUNTRY)

-patient age and sex (AGE, SEX)

-patient's total daily dose of vaccine at the time of the initial ADR (DOSE)

-the start date of therapy (THER START)

-the stop date of therapy (THER STOP)

-the date of onset of the ADR (ONSET)

-vaccine relationship provided by the investigator for study reports (DR)

- -(Y) yes (definite, probable possible)
- -(N) no (probably not, definitely not)
- -(U) unknown or blank

-serious (SER)-(Y) yes, -(N) no

-ADR term (with the notation # for any that are a worsening of a pre-existing condition)

-outcome from the ADR (RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE, RECOVERING/RESOLVING, NOT RECOVERED/NOT RESOLVING, FATAL, UNKNOWN)

All cases submitted individually on an expedited basis to one or more regulatory authorities have been marked with an asterisk beside the company reference number.

Changes to Reference Safety Information

There were no safety-related changes made to the International Physician's Circular (IPC) during the time period of this report; however, there were safety related changes made to the IPC after the data lock point which are described below:

CONTRAINDICATIONS

A statement regarding hypersensitivity to vaccine components, including gelatin, was added for consistency with other vaccine labels.

The egg hypersensitivity information was deleted since an egg hypersensitivity is no longer considered an absolute contraindication to vaccination with M-M-R II. Revised information now appears under PRECAUTIONS, Hypersensitivity to Eggs (see below).

References in the paragraph on immunocompromised individuals were deleted and a second sentence regarding measles inclusion body encephalitis (MIBE), pneumonitis and death as a direct consequence of disseminated measles vaccine virus infection in severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine was added based on published literature.

SIDE EFFECTS

This title of this section was revised from "ADVERSE REACTIONS" to "SIDE EFFECTS" per IPC format.

Under the "RARE" category:

- Body as a Whole

- "Atypical measles" was moved from the last paragraph in the section to this category.
- "Syncope, irritability" were added based on post-marketing reports.

- Hypersensitivity

- "Angioneurotic edema", "bronchial spasm" and related text were added based on post-marketing reports.

- Nervous/Psychiatric

- "Polyneuropathy" and "measles inclusion body encephalitis" were added based on post-marketing reports. Also the reference within the text was deleted.

- Respiratory System

- "Pnuemonitis, cough, rhinitis" were added based on post-marketing reports.
  - Skin
- "Stevens-Johnson syndrome" was added based on post-marketing reports.
- "Vesiculation at injection site, swelling" were moved from the last paragraph in the section.
  - Other
- Information regarding death from unknown causes was added based on published literature.

The IPC is the Company Core Data Sheet (CCDS) which contains the Company Core Safety Information (CCSI), indications, dosage, pharmacology, and other product information. The current IPC is included in Appendix 8.

Overall Safety Evaluation

The data presented in this safety supplement represent the marketed and clinical study experience with measles, mumps and rubella virus vaccine for reports that meet the criteria described in the "Description of Data Presented" section that were received by Merck & Co., Inc., from worldwide sources, between 01-Jan-1999 to 31-Dec-1999.

A large number of cases were reported from the United Kingdom as "condition unspecified". These are related to advise publicity in the lay press which has generated pending litigation.

Most of the ADRs reported during the period of this safety supplement are either already listed in the IPC or represent situations for which conclusions cannot be drawn such as very rare clinical syndromes of unknown etiology that also occur in unvaccinated individuals as well. Those events which are unlisted have been reviewed against cumulative data and relevant safety-related issues are summarized in this section.

Overall Conclusion

Examination of the data contained within this safety supplement supports the conclusion that measles, mumps and rubella virus vaccine is generally well tolerated. Analysis of these data supports the adequacy of the current CCDS in terms of product safety.

As with all Merck & Co., Inc. products, the safety profile of measles, mumps and rubella virus vaccine is closely monitored on a continuing basis.