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GENEESMIDDELEN

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MEDICINES
EVALUATION
BOARD

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Merck Sharp & Dohme B.V.
Postbus 581
2003 PC Haarlem

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Uw brief
03-04-2000

Uw kenmerk
[redacted]/MMR99

Den Haag,
29 augustus 2000

Zaaknummer
20007378007

Ons kenmerk/Coll
20007378[redacted] / 20016147

Behandeld door
[redacted]

Doorkiesnummer
[redacted]

Onderwerp
PSUR MMR-II (RVG 17672)

Naar aanleiding van uw bovenvermelde brief bericht ik u dat het ingezonden periodic safety update report over de periode 1 januari 1999 tot 31 december 1999 over de producten

M-M-R II, poeder voor injectievloeistof **RVG 17672**

vooralsnog geen aanleiding geeft tot aanpassing van deel IB. Wel vraag ik graag uw aandacht voor de volgende opmerkingen (in het Engels).

- In future PSURs the you should discuss the exposure to the vaccine in the reviewed period and the total number of reported cases in the reviewed period should be mentioned. In addition clinically relevant cases should be discussed.
- You should closely monitor the following areas and should submit a cumulative review in the next PSUR: autism and infectious meningitis.
- From this PSUR it has remained unclear why you have added the rare occurrence of the following side effects in the CCDS: angioneurotic oedema, bronchial spasm, polyneuropathy, measles inclusion body encephalitis, rhinitis and Stevens-Johnson syndrome. You should forward more information on these matters, i.e. reported cases should be discussed. You should also submit publications on inadvertently vaccinated immunocompromised patients.

Ik verzoek u om met bovengenoemde punten rekening te houden bij het inzenden van de volgende PSUR.

Namens het College ter beoordeling
van geneesmiddelen

drs. [redacted]

CONFIDENTIAL

COLL.NR:20007378(007)

X Nationale procedure
O Decentrale procedure
O Centrale procedure
Europees nummer
O Art.12 procedure

O Eindrapport
O Slot rapport
X Advies rapport

X Afhandeling secretariaat
O Overleg voorzitter
O Naar collegevergadering
O Kopie CPMP leden
O Kopie [redacted] IGZ

Section [redacted]

Date: 22-08-2000
Revised.

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Product name	: MMR-II		
Pharmaceutical form	: Powder for injection	**RVG NR**	17672 (=18676)
Active constituent	: Morbili vivi Paramyxovitus parotiditis vivus Rubellae vivum attenuatum	**ATC**	J07BD52
Applicant	: Aventis Pasteur MSD / Belgium	**PSUR**	1-1-1999 to 31-12-1999
Manufacturer	: [redacted]	**BirthDate**	02-12-1993

Introduction

MMR-II is a life virus vaccine and indicated for simultaneous immunisation against measles, mumps and rubella in humans of at least 15 months old. The MAH has submitted a five-years' PSUR *Periodic safety update report for MMR-II. Period of the report: 01 January 1999 – 31 December 1999 (not signed).*

Summary

To date MMR-II has been registered in multiple countries worldwide. In this PSUR no patient exposure or sales data have been estimated. Previous report from 1997 showed approximately [redacted] treated patients, of which over [redacted] in the USA in one year.

Assessor-s comment: in future PSURs the MAH should always submit exposure data on the period covered by the PSUR.

No regulatory or manufacturer's actions have been taken for safety reasons during the period of review.

However, the MAH made safety related changes in the company core data sheet after the data lock point, e.g.:

- as contra-indication a statement regarding 'hypersensitivity to vaccine components, including gelatin' was added for consistency to other vaccine labels
- the egg hypersensitivity information was removed as absolute contra-indication and revised information was replaced under the section precautions
- 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
- based on postmarketing studies the following rare side effects were added: syncope, irritability, angioneurotic oedema, bronchial spasm, polyneuropathy, measles inclusion body encephalitis, pneumonitis, cough, rhinitis, Stevens-Johnson syndrome

During the review period 1999 worldwide the MAH received 430 spontaneous reports on unlisted reactions, of which 246 non-serious reactions and 184 serious events. See table 1 for more information. Nine of the serious events resulted into death because ofaplastic anemia, gastro-intestinal bleeding, epilepsy (2x), fever, cardiac arrest, infectious meningitis or unknown cause (2x).

772 listed reactions were spontaneously received by the MAH: mostly concerning fever or skin reactions.

Within clinical research setting three serious drug related events have been reported: infectious meningitis, cough (both unlisted) and febrile seizure (listed).

None of the reported adverse drug reactions occurred in The Netherlands.

Assessor-s comment: No descriptions of case histories are included. In future PSURs the MAH should discuss clinically relevant case histories. The MAH should also provide the number of reports on all cases and not only on serious cases. The PSUR encloses a summary tabulation of listed reactions, which can be an overestimation due to one report consisting of events in more than one body-system.

TABLE 1

Summary tabulation of unlisted reactions if ≥ 5x spontaneously reported in 1999			
body system	**reactions**	**number**	**of which serious**
body as a whole	asthenia/fatigue	15	-
	crying	5	-
	edema	14	2
	injection site induration wider than 1 inch	7	-
	injection site wheal	6	-
	lack of response	6	-
	pain	8	2
	syncope	7	2
cardio-vascular	petechia	5	1
metabolism & nutrition	weight loss	5	1
nervous	gait abnormality	13	5
	hypotonia	6	5
	somnolence	6	3
psychiatric	autism	6	6
	irritability	16	2
respiratory	cough	8	2
	dyspnea	6	1
skin	exanthema	20	2
	pruritus	10	1
	varicella	6	-

The MAH also provided a cumulative overview on the unlisted serious reactions (see Table 2).

TABLE 2

Cumulative summary tabulation of unlisted serious reactions if ≥ 10x spontaneously reported		
body system	**reactions**	**number**
body as a whole	asthenia/fatigue	26
	dehydration	12
	edema	13
	lack of response	11
	reaction	12
	syncope	17
	unknown cause of death	15
	upper respiratory infection	13
	viral infection	11
cardio-vascular	cyanosis	11
digestive	pancreatitis	12
endocrine	diabetes mellitus	24
nervous	gait abnormality	21
	grand mal seizures	11
	hypotonia	10
	infectious meningitis	31
psychiatric	autism	47
	irritability	10
respiratory	cough	10
	pneumonia	12
skin	exanthema	19
other	therapeutic abortion	16

* Tabulated from 696 reports in total

Assessor-s comment: From this PSUR it has remained unclear why the MAH added the rare occurrence of the following side effects in the CCDS: angioneurotic oedema, bronchial spasm, polyneuropathy, measles inclusion body encephalitis, rhinitis and Stevens-Johnson syndrome. The MAH should forward more information; reported cases should be discussed.

The MAH should submit publications on inadvertently vaccinated immunocompromised patients.

Exanthema has been mentioned as undesirable effect in the present IB-text.

Publications have been listed but not discussed in this PSUR. Especially from this PSUR it cannot be assessed if the text on hypersensitivity to eggs as adapted in the CCDS

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should be changed in the Dutch IB-text. However, in line with the IB-text of a similar products (RVG17654, RVG 22052) and considering literature the anaphylactoid reaction to eggs should be removed as contra-indication and the revised information on hypersensitivity to eggs should be added under the section precautions of the SPC. (RJF Burgmeijer, JAM Merkx. Vaccinaties bij kinderen in perspectief – Voorjaarssymposium Ouder en Kindzorg 1996. JM James, A Wesley Burks, et al. Safe administration of the measles vaccine to children allergic to eggs. N Engl J Med 1995;332:1262-6)

Based on their reported frequencies the following rare undesirable effects should be monitored closely: infectious meningitis, autism. Cumulative reviews discussing the reported cases should be submitted in the next PSUR.

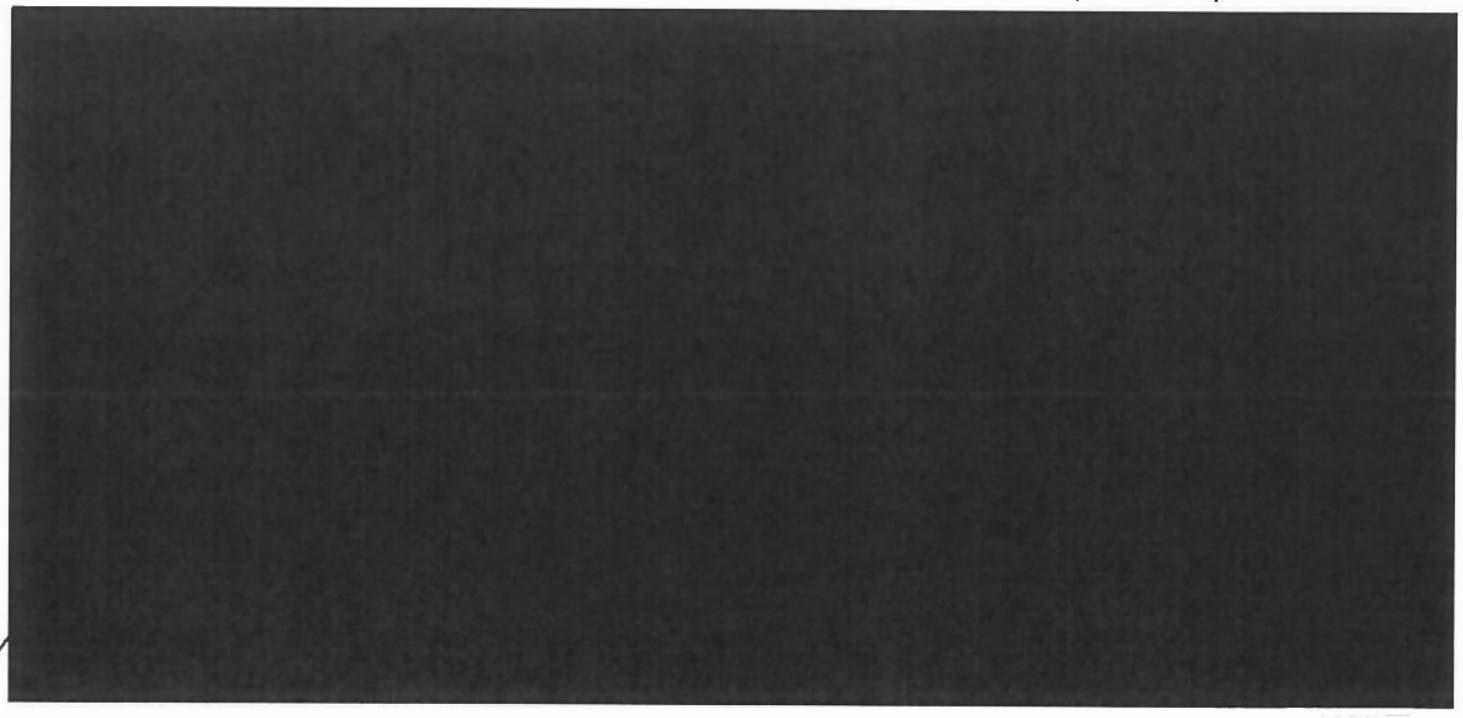
Furthermore, in line with the IB-text of similar products information regarding 'HIV-infected patients with minor to moderate immunedeficiency MMR vaccination can be indicated (to avoid measles, often with fatal outcome in these patients)' should be added to the SPC.

And finally, the statement 'hypersensitivity to any component of the vaccine, including gelatin' should be added in the SPC at section contra-indications.

Conclusions

Periodic safety update report for MMR-II. Period of the report: 01 January 1999 – 31 December 1999 has been assessed. The company's core data sheet has recently been updated. The following remarks are relevant:

- In future PSURs the MAH should discuss the exposure to the vaccine in the reviewed period and the total number of reported cases in the reviewed period should be mentioned. In addition clinically relevant cases should be discussed.
- The MAH should closely monitor the following areas and should submit a cumulative review in the next PSUR: autism, and infectious meningitis.
- From this PSUR it has remained unclear why the MAH added the rare occurrence of the following side effects in the CCDS: angioneurotic oedema, bronchial spasm, polyneuropathy, measles inclusion body encephalitis, rhinitis and Stevens-Johnson syndrome. The MAH should forward more information on these matters, i.e. reported cases should be discussed. The MAH should also submit publications on inadvertently vaccinated immunocompromised patients.



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