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COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

CBG MEB

MEDICINES EVALUATION BOARD

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Uw brief
20 juni 2000

Uw kenmerk
[redacted]00 170

Den Haag,
1 juli 2002

Zaaknummer
20012174005

Ons kenmerk/Coll
20012174[redacted]1/0110/ 2021378 2

Behandeld door
[redacted]

Doorkiesnummer
[redacted]

Onderwerp
M-M-R II

With regard to your safety update report, summarising safety data from 1 januari 1996 up to 31 december 1999 voor concerning

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

I inform you as follows:

1) You are requested to submit a discussion of the fatal cases.

2) In view of the recent changes in the CCSI as well as some additional information in this PSUR you should submit, data, literature and a discussion on the following issues: inadvertently vaccinated immunocompromised patients, thrombocytopenia, Stevens Johnson Syndrome, syncope, irritability, (angioneurotic) oedema, bronchospasm, cough, rhinitis, polyneuropathy, measles inclusion body encephalitis (MIBE), pneumonitis, and death from various and in some cases unknown causes (including 'sudden infant death').

3) You should provide a cumulative overview and detailed discussion of nervous and psychiatric events (including 'autism' and 'infectious meningitis').

4) The summary table of spontaneous unlisted events (Appendix 2 Table 1 - 12 pages) was incomplete. It stopped at Nervous System - 'hypotonia'. You are requested to submit the missing part of the table to enable a proper safety assessment.

5) You should submit a proper overall safety evaluation, focussing on severe signs or symptoms of measles, mumps, rubella and well-known complications of these diseases (e.g. pancreatitis, myocarditis) and the possibility of vaccine-inducement in these cases.

6) You should provide information on the relevant cases in the litigation in the UK within the next 3 months.

7) In next PSUR you should clarify the term 'product exposure'. You are also requested to clarify whether the cases of drug overdose, product misuse, product abnormality, product confusion, product exposure and use of outdated product had any signs or symptoms and you should submit a proper safety evaluation of these cases.

8) In next PSUR you should submit a cumulative review of unwanted effects related to exposure during pregnancy.

10) Furthermore you should submit a proposal for an EU birth date and a revised PSUR-cycle.

11) Future PSURs should be in line with all aspects of ICH Guideline E2C, including registration and marketing authorisation status, specification of total number of reports received during the review period, discussion of clinically relevant cases, literature review.

12) Furthermore you are requested to mention the RVG number of the product in your letter.

I would like to receive your response as soon as possible, but not later than 1 October 2002.

On behalf of the Medicines
Evaluation Board in the Netherlands

[redacted]

C

CONFIDENTIAL

COLL.NR: 20012174(005).

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 V: [redacted]

Date: 20 June 2002
Revised:

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Product name	M-M-R II	**RVG NR**	17672
Pharmaceutical form	Powder for injection	**ATC**	JO7BD52
Active constituent	Live attenuated measles, mumps and rubella viruses	**PSUR**	1-Jan-96 to 31-Dec-99
Applicant	MSD [redacted] NL	**BirthDate**	IBD: 15-Sep-1978 (USA)
Manufacturer	[redacted]		NL: 2-Dec-1993

Introduction

M-M-R II is a live mumps-measles-rubella vaccine. It consists of powder for reconstitution and injection.

M-M-R II is indicated for simultaneous immunisation against measles, mumps and rubella in persons aged 15 months or older. A repeat dose of M-M-R II or monovalent vaccine is recommended.

On 3 April 2000 Merck Sharpe & Dohme B.V. submitted a PSUR that covered the period from 1 January 1996 to 31 December 1999 (not signed, not dated). The product was first registered in the Netherlands on 2 December 1993. The MAH did not provide the international birth date of M-M-R II.

Assessor's comment: For unknown reasons the PSUR covered a 4-yearly period. Also, duplicate data were submitted for 1997 and for 1999, since the MAH had previously submitted a PSUR for the period from 1 January to 31 December 1997 (collnr. 9814061) and a PSUR for the period from 1 January 1999 to 31 December 1999 (collnr. 20007378).

The MAH should submit a proposal for an EU birth date and a revised PSUR-cycle (a letter has been sent to all MAH to request an EU birth date for their products).

Summary

The MAH did not provide information on registration and marketing status during the period covered by the PSUR.

Assessor's comment: In the future the MAH should submit these data (cumulatively) with the PSUR.

The MAH stated that no safety-related changes were made to the Company Core Data Sheet (CCDS / CCSI) during the period of the PSUR, however, they had made safety-related changes to the CCDS / CCSI after the data lock point according to the MAH himself "based on post-marketing reports".

Assessor's comment: The CCSI (Company Core Safety Information) included safety data that were not covered in the Dutch SPC, i.e.:

- *Contraindications included hypersensitivity to any component of the vaccine, including gelatin. Egg hypersensitivity was removed. The paragraph on immunocompromised individuals was removed and information on measles inclusion body encephalitis (MIBE), pneumonitis and death as direct consequence of disseminated measles vaccine virus infection in severely immunocompromised individuals who were inadvertently vaccinated with measles containing vaccine was added based on published literature.*
- *Precautions included thrombocytopenia, and revised text concerning egg hypersensitivity.*
- *Side effects included Stevens Johnson Syndrome, syncope, irritability, angioneurotic edema (including peripheral or facial edema), bronchospasm, cough, rhinitis, polyneuropathy, measles inclusion body encephalitis (MIBE), pneumonitis, and death from various and in some cases unknown causes.*

The CCSI should only contain information that has been approved in all countries where the product is registered. Therefore, if the MAH deems it necessary to amend the CCSI, the national SPCs should reflect this. It is noted that the PSUR supports inclusion of several terms of the recent update of the CCSI, but due to the poor quality of this PSUR a final decision cannot be made. Within the next 3 months the MAH should submit data, literature and a discussion on the above-mentioned changes to enable assessment on necessity of inclusion into the Dutch SPC. It should be noted that in August 2000 such request for additional information on these issues was also made (without mentioning a deadline) without any response from the MAH up to now.

Furthermore, section 4.3 'Contra-indications' of the Dutch SPC should be updated to replace "Anafylactische of anafylactoïde reactie op neomycine" by "Systemische overgevoeligheid

voor neomycine, gelatine of één van de andere componenten van het vaccin."

Additionally, as already concluded in the PSUR AR dated 22-08-2000: In line with the IB-text of similar products (RVG 17654, RVG 22052) licensed in The Netherlands and considering literature (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) the Dutch SPC should be updated, i.e. the anaphylactoid reaction to eggs should be removed from section 4.3 'Contra-indications' and the revised information on the hypersensitivity to eggs should be added under the section precautions of the SPC: "Bof- en mazelenvirus worden gekweekt in cellen afkomstig van kippenembryo's. Overgevoeligheid voor kippeneiwit is geen contra-indicatie. Vaccinatie kan worden overwogen bij patiënten die bekend zijn met anafylactoïde reacties op kippeneiwit. Tevens wordt geadviseerd epinefrine (adrenaline) en corticosteroïden beschikbaar te hebben en zonodig, gedoseerd naar leeftijd en/of lichaamsgewicht toe te dienen."

The number of doses distributed from 1 January 1996 to 31 December 1999 was [redacted].

Assessor's comment: For this safety assessment of the PSUR, the assessor assumed that patients received two doses of MMR-II each and therefore that exposure was [redacted] patients.

The MAH did not submit information about the total number of reports they received during the period covered by the PSUR. However the assessor-s counted more than 3,200 spontaneous reports of which more than 650 were serious and 37 were fatal.

Assessor's comment: In future PSURs the MAH should provide information about the total number of reports received during the period covered by the PSUR.

The PSUR did not include either a discussion of safety nor CIOMS forms nor comments to individual reports in the line listings.

Assessor's comment: The assessor's safety assessment was based solely on period summary tabulations and line listings (coded terms only, no comments).

The most frequent events are summarised in table 1. A cut-off for the frequency of each type of event (serious/non-serious and listed/unlisted) was chosen based on an estimated exposure of [redacted] patients. Non-serious unlisted events are included in the table if an event occurred 500 times or more. The assessor chose this figure in order to detect an increase in frequency above 1:100,000.

The 37 reports with fatal outcome concerned: encephalitis (1), infectious meningoencephalitis (1), spontaneous abortion (7), fetal death (1), induced abortion (condition) (2), therapeutic abortion (6), abortion unspecified (1) *(Assessor-s comment: these are sufficiently covered by the SPC, see also assessor-s comment after the paragraph on exposure during pregnancy)*, as well as thrombocytopenic purpura (1), bacterial infection/thrombocytopenic purpura (1), viral pneumonia (1), general deterioration/unknown cause of death (1), unknown cause of death (5), sudden infant death syndrome (3), airway obstruction/unknown cause of death (1), cardiac arrest (1), left cardiac failure (1), aplastic anemia (1), head trauma (1) and asphyxiation (1).

Assessor-s comment: Within 3 months the MAH should submit a discussion of the fatal cases. Concerning thrombocytopenic purpura: see previous assessor-s comment on thrombocytopenia that the MAH should submit data, literature and a discussion on this issue following the inclusion in the CCSI. Within 3 months the MAH should provide a cumulative overview and discussion on reports of sudden infant death syndrome as well as unknown cause of death, also taking into account that the CCSI was updated to include 'death from various and in some cases unknown causes' as reported event.

The most frequently reported serious unlisted events were asthenia/fatigue (13), gait abnormality (14), syncope (7), unknown cause of death (7), upper respiratory tract infection (7). Angioedema occurred 8 times (2 serious and 6 non-serious). Cumulative serious unlisted events included a large number of nervous events (169) and psychiatric events (69, including 47 cases of autism).

Assessor-s comment: Asthenia/fatigue (13), gait abnormality (14) are sufficiently covered by 'malaise' and 'ataxia' in the SPC. A number of serious unlisted events occurred 2-6 times (see table for details). Some of these are already sufficiently covered by a different wording in the SPC (e.g. hyperthermia, petechia), others may be incidental cases.

Concerning angiooedema, bronchospasm, pneumonitis, cough, and rhinitis: see previous assessor-s comment (PSUR AR dated 22-08-2000).

Furthermore the MAH should provide a cumulative overview and detailed discussion of nervous and psychiatric events within the next 3 months (in view of the large total number of nervous and psychiatric events and the recent inclusion of polyneuropathy in the CCSI). It should be noted that in August 2000 a request was made that the MAH would provide a cumulative overview and discussion on the reports of autism and infectious meningitis.

The most frequently reported serious listed event were fever (42), thrombocytopenia (32), thrombocytopenic purpura (41), febrile seizures (110), seizure (63) and rash (44). Additionally within clinical trial setting two serious, vaccine-related : febrile seizures (1) and rash (1) were reported.

Assessor-s comment: Based on an estimated exposure of [redacted] patients, these events had a reported frequency rate of less than 1:1,000,000. Regarding frequency rates the serious listed events were therefore sufficiently covered by current SPC.

The most frequently reported non-serious unlisted events included: condition unspecified (67), asthenia/fatigue (82, of which 13 serious), edema (39, of which 4 serious), gait abnormality (51, of which 14 serious).

The most frequent non-serious listed event was 'fever (747). Based on an estimated patient exposure of [redacted] patients, all non-serious listed events had a reported frequency rate of less than 1:10,000 and were therefore sufficiently covered by the SPC.

Assessor's comment: The summary table of spontaneous unlisted events submitted by the MAH (Appendix 2 Table 1 - 12 pages) was incomplete. It stopped at Nervous System - 'hypotonia'. The MAH should submit the missing part of the table for a proper safety assessment.

For further assessment of unlisted events (serious and non-serious), the missing part of the relevant period summary tabulation is awaited.

Furthermore, several events may be signs or symptoms of measles, mumps or rubella, or well-known complications of these diseases (e.g. pancreatitis – cumulatively at least 12 reports - or myocarditis – cumulatively at least 8 reports). Therefore, within the next 3 months the MAH should submit a proper overall safety evaluation, focussing on severe signs or symptoms of measles, mumps, rubella and well-known complications of these diseases (e.g. pancreatitis, myocarditis) and the possibility of vaccine-inducement in these cases.

The period summary tabulations included 3 reports of lack of response (cumulative 11 reports).

No reports on drug interactions were submitted in the PSUR.

The MAH reported serious drug overdose (5), outdated product use (45), product misuse (105, of which 1 serious), product abnormality (2), product confusion (4) and product exposure (12).

Assessor's comment: In next PSUR the MAH should clarify the term 'product exposure'. Also, as no information was provided as to whether these patients experienced any signs or symptoms, it was impossible to make a proper safety assessment. The MAH should clarify whether the cases of drug overdose, product misuse, product abnormality, product confusion, product exposure and use of outdated product had any signs or symptoms and should submit a cumulative overview and discussion of these reports with the next PSUR.

The MAH did not submit a cumulative review of unwanted effects related to exposure during pregnancy. The period tabulation of unlisted events included spontaneous abortion (7), foetal death (1), induced abortion (condition) (2), therapeutic abortion (6), abortion unspecified (1), congenital anomaly (1 - cumulative 5). However note that part of this table was missing.

Assessor's comment: The MAH should submit a cumulative review of unwanted effects related to exposure during pregnancy in the next PSUR.

The MAH submitted a list of references, but not a discussion of relevant literature.

Assessor's comment: The MAH should submit a discussion of all relevant publications.

Finally the MAH stated that there was pending litigation in the UK.

Assessor's comment: The MAH should provide information on the relevant cases within the litigation in the UK.

Additional comments with regard to the Dutch SPC

As already concluded in the PSUR AR dated 22-08-2000: In line with the IB-text of similar products licensed in The Netherlands the following information should be added in section 4.4 'Speciale waarschuwingen' of the Dutch SPC: *"Bij HIV-patiënten met ernstige immuundeficiënties komen vaccinatie gerelateerde complicaties voor. Aan hen wordt MMR-II dan ook niet toegediend; bij contacten van dergelijke patiënten met mazelen wordt profylaxe aanbevolen met normaal immunoglobuline. Bij HIV-geïnfecteerde patiënten met lichte tot matige immuundeficiëntie kan BMR vaccinatie aangewezen zijn (ter voorkoming van vaak fataal verlopende mazelen bij deze patiënten)."*

As already concluded in the PSUR AR dated 22-08-2000: The information in section 4.3 'Contraindications': "Primaire en verworven immunodeficiënties, zoals patiënten met immunosuppressie in samenhang met AIDS of andere klinische manifestaties van infectie met humane immunodeficiëntievirussen; cellulaire immunodeficiëntie, hypogammaglobulinemie en dysgammaglobulinemie." should be followed by " (zie ook Speciale waarschuwingen en bijzondere voorzorgen bij gebruik)."

Conclusions

The PSUR covering the period from 1 January 1996 to 31 December 1999 (not signed, not dated) was assessed. Due to lacking information a full assessment could not be made. However the following conclusions have been drawn:

1) In line with the IB-text of similar products (RVG 17654, RVG 22052) licensed in The Netherlands and considering literature (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) the Dutch SPC should be updated: the anaphylactoid reaction to eggs should be removed as absolute contra-indication and the following information on the hypersensitivity to eggs should be added under the section precautions of the SPC: *"Bof- en mazelenvirus worden gekweekt in cellen afkomstig van kippenembryo's. Overgevoeligheid voor kippeneiwit is geen contra-indicatie. Vaccinatie kan worden overwogen bij patiënten die bekend zijn met anafylactoïde reacties op kippeneiwit. Tevens wordt geadviseerd epinefrine (adrenaline) en corticosteroïden beschikbaar te hebben en zonodig, gedoseerd naar leeftijd en/of lichaamsgewicht toe te dienen".*

2) In line with the IB-text of similar products licensed in The Netherlands the following information should be added in section 4.4 'Speciale waarschuwingen' of the Dutch SPC: *"Bij HIV-patiënten met ernstige immuundeficiënties komen vaccinatie gerelateerde complicaties voor. Aan hen wordt MMR-II dan ook niet toegediend; bij contacten van dergelijke patiënten met mazelen wordt profylaxe aanbevolen met normaal immunoglobuline. Bij HIV-geïnfecteerde patiënten met lichte tot matige immuundeficiëntie kan BMR vaccinatie aangewezen zijn (ter voorkoming van vaak fataal verlopende mazelen bij deze patiënten)."*

3) The information in section 4.3 'Contraindications': "Primaire en verworven immunodeficiënties, zoals patiënten met immunosuppressie in samenhang met AIDS of andere klinische manifestaties van infectie met humane immunodeficiëntievirussen; cellulaire immunodeficiëntie, hypogammaglobulinemie en dysgammaglobulinemie." should be followed by "(zie ook Speciale waarschuwingen en bijzondere voorzorgen bij gebruik)."

4) Section 4.3 'Contra-indications' of the Dutch SPC should be updated to replace "Anafylactische of anafylactoïde reactie op neomycine" by "Systemische overgevoeligheid voor neomycien, gelatine of één van de andere componenten van het vaccin."

5) Within 3 months the MAH should submit a discussion of the fatal cases.

6) In view of the recent changes in the CCSI as well as some additional information in this PSUR the MAH should submit, within the next 3 months, data, literature and a discussion on the following issues: inadvertently vaccinated immunocompromised patients, thrombocytopenia, Stevens Johnson Syndrome, syncope, irritability, (angioneurotic) edema, bronchospasm, cough, rhinitis, polyneuropathy, measles inclusion body encephalitis (MIBE), pneumonitis, and death from various and in some cases unknown causes (including 'sudden infant death').

7) Within the next 3 months the MAH should provide a cumulative overview and detailed discussion of nervous and psychiatric events (including 'autism' and 'infectious meningitis').

8) The summary table of spontaneous unlisted events submitted by the MAH (Appendix 2 Table 1 - 12 pages) was incomplete. It stopped at Nervous System - 'hypotonia'. Within the next 3 months the MAH should submit the missing part of the table to enable a proper safety assessment.

9) Within the next 3 months, the MAH should submit a proper overall safety evaluation, focussing on severe signs or symptoms of measles, mumps, rubella and well-known complications of these diseases (e.g. pancreatitis, myocarditis) and the possibility of vaccine-inducement in these cases.

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10) The MAH should provide information on the relevant cases in the litigation in the UK within the next 3 months.

11) In next PSUR the MAH should clarify the term 'product exposure'. Also, the MAH should clarify whether the cases of drug overdose, product misuse, product abnormality, product confusion, product exposure and use of outdated product had any signs or symptoms and should submit a proper safety evaluation of these cases.

12) In next PSUR the MAH should submit a cumulative review of unwanted effects related to exposure during pregnancy.

13) The MAH should submit a proposal for an EU birth date and a revised PSUR-cycle.

14) Future PSURs should be in line with all aspects of ICH Guideline E2C, including registration and marketing authorisation status, specification of total number of reports received during the review period, discussion of clinically relevant cases, literature review.

Note to the Secretariat:

[redacted]

Table 1: Serious and non-serious unlisted reports by System Organ Class (company dictionary)

SOC	Serious listed (ADR >= 10 times)	Serious unlisted (ADR >= 2 times/ cumulative figure)	Non-serious (ADR >= 500 times)	Non-serious unlisted (ADR >= 10 times)
Body as a whole/ site unspecified	**169** Fever=42	**106** Asthenia/fatigue=13/26 Dehydration=5/12 Drug overdose=5/7 Edema=4/13 Hyperthermia=3/4 Sudden infant death syndrome=3/8 Syncope=7/17 Unknown cause of death=7/15 Upper respiratory tract infection=7/13 Vasovagal reaction=3/4 Viral infection=6/11	**1037** Fever=747	**626** Condition unspecified=67 Abdominal pain=22 Asthenia/fatigue=69 Body as a whole/site condition unspecified=10 Crying=12 Edema=35 Injection site wheal=19 Lack of response=18 Outdated product use=45 Pain=23 Product exposure=12 Product misuse=104 Upper respiratory infection=18
Cardiovascular system	**4**	**32** Cardiovascular disorder=3/3 Cyanosis=6/11 Hematoma=3/4 Myocarditis=2/8 Petechia=4/5	**8**	**45** Petechia=14
Digestive system	**38** Vomiting=17	**28** Gastroenteritis=4/5 Inflammatory bowel disease=2/2 Pancreatitis=6/12 Ulcerative colitis=2/2	**274**	**86** Colitis=12
Endocrine system	**0**	**7** Diabetes mellitus=3/24 Insulin-dependent diabetes mellitus=2/3	**0**	**2**
Eyes, ears, nose and throat	**33** Hearing loss=14	**31** Ophtalmic movement disorder=3/4	**112**	**127** Nasal secretion=21 Tonsillitis=13

SOC	Serious listed (ADR >= 10 times)	Serious unlisted (ADR >= 2 times/ cumulative figure)	Non-serious * (ADR >= 500 times)	Non-serious unlisted (ADR >= 10 times)
Hemic and lymphatic system	**95** Lymphadenopathy=15 Thrombocytopenia=32 Thrombocyopenic purpura=41	**30** Aplastic anemia=2/3 Blood dyscrasia=2/2 ESR increased=2/7 Hemolytic anemia=2/5 Leukocytosis=3/9 Leukopenia=6/8 Splenic disorder=2/5	**199**	**21**
Hepatobiliary system	**0**	**8** Hepatic function abnormality=2/7	**0**	**6**
Immune system	**16** Anaphylaxis=13	**5** Angioedema=2/6	**24**	**17**
Metabolism and nutrition	**0**	**14** Aminotransferase increased=2/2 Hyperglycemia=3/3	**0**	**41** Appetite change=11
Musculoskeletal system	**24** Arthralgia=12	**14** Juvenile chronic arthritis=3/6 Muscular atrophy=2/2 Systemic lupus erythematosus=2/2	**87**	**81** Arm pain=10
Nervous system	**223** Encephalitis=19 Encephalopathy=10 Febrile seizure=110 Seizure=63	**57?** Aphasia=2/3 Brain disorder=3/4 Brain stem disorder=2/2 Cerebellar disorder=4/4 EEG abnormality=2/2 Facial paralysis=3/3 Flaccid paralysis=2/2 Gait abnormality=14/21 Grand mal seizure=5/11 Hypotonia=8/10 **?** **Missing part of summary table**	**157**	**88?** **Missing part of summary table**

SOC	Serious listed (ADR >= 10 times)	Serious unlisted (ADR >= 2 times/ cumulative figure)	Non-serious * (ADR >= 500 times)	Non-serious unlisted (ADR >= 10 times)
Psychiatric disorder	**0**	**?**	**0**	**?**
Respiratory system	**0**	**?**	**0**	**?**
Skin and skin appendages	**80** Morbilliform rash=15 Rash=44 Urticaria=13	**?**	**915**	**?**
Urogenital system	**1**	**?**	**15**	**?**