CBG
MEB

Zaaknummer: 20702406019, 20702406020

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M-M-R II
(MEASLES, MUMPS AND RUBELLA VIRUS VACCINE LIVE)

ASSESSMENT REPORT

25-08-2008

Pharmaceutical form(s)	Powder for fluid for injection Rubella 1000 TCID50/flask Mumps 5000 TCID50/flask Measles 1000 TCID50/flask
MAH(s)	Sanofi Pasteur MSD
Document	Response
Assessor	[redacted]
Contact point	[redacted]

Introduction

The MAH submitted a response to comments made by the MEB concerning issues raised in the previous PSUR assessement and included a type II variation.

Assessment of the response document

o MEB comment

Sections 4.2, 4.3, and 4.8 of the current Core Safety Information (CSI) provide more (relevant safety) information than the Dutch SPC. The MAH should note that a Core Safety Information can not contain information which is not included in at least every accepted national SPC. If the MAH deems it necessary to include this information in the CSI the MAH should submit an adequately supported application for inclusion of this information and a proposal to update the Dutch SPC. If correctly used the Core Safety Information cannot include information which is not accepted in all countries where a product is licensed.

Response by the MAH

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The MAH submitted an application for harmonisation of the SPC of MMR III with the SPC of MMRvaxPro which was accepted. In the current submission a proposal to update section 4.8 is included.

Assessor's comment: Issue resolved, a proposal to update section 4.8 of the SPC is included.

MEB comment
Regarding section 4.8. The MAH submitted an application for harmonisation of the SPC of MMR II with the SPC of MMRvaxPro. It was noted however, that the MAH had not included the adverse reactions Toxic Epidermal Necrolysis (TEN) and pancreatitis as asked in our letter of the 9th April 2003 coll 20221015. The assessor for the application for Type II variation to harmonize SPC of M-M-RII with the SPC of M-M-RvaxPro made the following conclusion: harmonisation of the SPCs is accepted provided that the MAH will still consider Toxic Epidermal Necrolysis (TEN) and pancreatitis to be included in the Dutch SPC of M-M-RII (i.e. the decision to include these adverse reactions or the justification not to include, as was stated in the response document of the MAH are still being awaited) and with respect to pancreatitis, the MAH should at least explain why this adverse event is included in the American SPC but not in the Dutch SPC.

Response by the MAH
The adverse reaction Toxic Epidermal Necrolysis is not being included as we argued in our letter dated on May 10 2007 (AR/503) with the following argumentation: "The MAH is not in favour of adding "Toxic Epidermal Necrolysis" (TEN) in the CCDS/SPC. There are 4 reports of TENS (originally 5 reports of TENS but one was excluded as a result of streptococcal infection). For the 4 reports, there is no causative etiology for TENS (e.g. streptococcal infection). Although these cases are considered temporally associated with vaccination, the frequency of reports in the background population is similar to the frequency of reports for doses of M-M-R™ distributed. Frequency of TENS in general population is roughly 0.4 to 1.2 cases per million person-years (appendix 1), and there are 4 reports for 500 million doses of M-M-R™II sold. The MAH will continue monitor all reports of TENS, should they receive them, at adverse experience reporting meetings (AERTs)."
The adverse reaction "pancreatitis" was already added in the current SPC on May 10, 2007.

Assessor's comment: Issues are considered resolved. Rationale not to include TEN is accepted provided that the MAH will continue close monitoring and will provide cumulative reviews in all upcoming PSURs. Pancreatitis is included in the current Dutch SPC dated 12 February 2008.

o MEB comment
The MAH should include the adverse reactions nasopharyngitis, upper respiratory infection, viral infection, rhinorrhoea, diarrhoea, vomiting to the SPC. And the MAH should include the adverse reactions, collapse or shock-like state (hypotonic-hyporesponsiveness episode), dermatitis, decreased appetite, prolonged or abnormal

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crying, restlessness, drowsiness, fatigue, lethargy, dyspnoea, pain in extremity, insomnia to their SPC as these are also an issue with other vaccines.

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Response by the MAH
The MAH is in favour of adding the following adverse reactions because they also appear in the EU SPC for M-M-RVAXPRO:
• nasopharyngitis, upper respiratory tract infection or viral infection
• rhinorrhoea
• diarrhoea or vomiting

The MAH is not in favour of adding the following terms because there are no data to support adding them to the Dutch label and because they are not terms that are present in the headquarters IPC or in the harmonized EU SPC for M-M-RVAXPRO:
• prolonged or abnormal crying, drowsiness, lethargy
• collapse or shock-like state (hypotonic-hyporesponsiveness episode), decreased appetite, restlessness, fatigue, insomnia, pain in extremity
• dyspnoea
• dermatitis

Assessor's comment: It was noted the text nasofaryngitis, infectie van de bovenste luchtwegen of virale infectie was accidentally included twice in the annotated version of the SPC (once in coloured text and once in normal text). Please make sure the text is included only once in the SPC.

o MEB comment
Although the MAH comments in the PSUR (01-01-2001 to 31-12-2005) safety analysis on the study protocol 011 will be provided in the next PSUR, this analysis can not be found in the addendum or the one year PSUR submitted concomitantly. The MAH should provide the safety analysis for study protocol 011 within 3 months.

Response by the MAH
The safety analysis of this study was provided in the 6-months PSUR covering the period of 05-nov-2006 to 04-may-2007 which was submitted to all MS in July 2007 in the scope of the M-M-RvaxPro license.
The MAH enclosed a copy of section 7.1 (Newly Analyzed Studies) as well as of Annex 10 (Clinical Study Report - Synopsis of Protocol [redacted])

Assessor's comment: The supporting documentation was submitted. No new safety issues were identified and the issue is considered resolved.

o MEB comment
The next PSUR covering the period, 01-01-2006 to 31-12-2008 should be submitted within 60 days after data lock point.

Response by the MAH

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We will not submit a PSUR covering the period 01-01-2006 to 31-12-2008 as it was agreed last year that a common PSUR will be submitted for both MMRII and M-MRvaxPro, according to the new PSUR cycle defined for M-M-RvaxPro following its new EU registration.

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Assessor's comment: Indeed, the MEB has previously commented that taking into account that the PSUR cycle is amended, this can be accepted. However, the MEB noted that it is anticipated that the MAH will distinguish into separate sections for M-M-R™II and M-M-RvaxPro® within 1 single PSUR. The distinction is necessary as M-M-RII contains human albumin and it can be anticipated that reactogenicity is different from M-M-RvaxPro that contains recombinant albumin.

Conclusions

Assessment of the response upon comments made by the MEB led to the following conclusions:

- It was noted the text nasofaryngitis, infectie van de bovenste luchtwegen of virale infectie was accidentally included twice in the annotated version of the SPC (once in coloured text and once in normal text). Please make sure the text is included only once in the SPC.
- Issues are considered resolved. Rationale not to include TEN is accepted provided that the MAH will continue close monitoring and will provide cumulative reviews in all upcoming PSURs.
- Indeed, the MEB has previously commented that taking into account that the PSUR cycle is amended, this can be accepted. However, the MEB noted that it is anticipated that the MAH will distinguish into separate sections for M-M-R™II and M-M-RvaxPro® within 1 single PSUR. The distinction is necessary as M-M-RII contains human albumin and it can be anticipated that reactogenicity is different from M-M-RvaxPro that contains recombinant albumin.

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