PRE-ICI:
COLL.NR: 20708821 (answer to comments)
Zaaknummer: 2060760317

Samen afgehandeld met:
COLL.NR: 20708823 (harmonisatie SPC)
Zaaknummer: 20708823020

X Nationale procedure
O Decentrale procedure
O Centrale procedure

O Eindrapport
O Slot rapport
X Advies rapport

X Afhandeling secretariaat
O Overleg voorzitter
O Naar collegevergadering
Kopie CHMP leden

FT4-PV: [redacted]

Date: 2007-05-08

COLLEGE
TER BEOORDELING VAN
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|---|---|---|---|---|
| **Product name** | : M-M-RII | | | |
| **Pharmaceutical form** | : | **RVG NR** | 17672=18676 | A10<br>A15a<br>C |
| **Active constituent** | : | **ATC** | | |
| **Applicant** | : | **PSUR** | Answer to comments | |
| **Manufacturer** | : [redacted] | **BirthDate** | | |

The MAH submitted:

- Answer to comments following 5-year PSUR submission: 1 January 2001 to 31 December 2005

Assessor's comment: For the assessment of the response, the MEB also takes into account:
- Application for Type II variation to harmonize SPC of M-M-RII with the SPC of M-M-RvaxPro
- Application for a renewal for M-M-RII

The comments that were given by the MEB on PSUR 1 January 2001 to 31 December 2005 with the corresponding answers of the MAH are listed below:

**Previous MEB comment:**

[redacted]

The submitted data revealed new safety information requiring amendments to the SPC: In the section 4.8 Undesirable effect Toxic Epidermal Necrolysis should be included.

**Answer of the MAH:**

The decision to add the adverse event "Toxic Epidermal Necrolysis" in the CCDS/SPC has to be discussed and assessed internally. The final decision will be taken end of April.
At that time we will communicate you the decision, with an updated SPC if decision is to add TEN, or with a justification if decision is to not add TEN.

**Assessor's comment: Issue not resolved**

**Previous MEB comment:**

In our letter of the 9th April 2003 coll 20221015 you were asked to make the following amendments to the Dutch SPC: in section 4.8 Undesirable effects should be included in: Pneumonia, Stevens Johnson syndrome, bronchospasme, irritability and pancreatitis.

**Answer of the MAH:**
Please note that in answer to this letter dated 09/04/2003, a PSUR was prepared and submitted, but unfortunately it seems it never reached MEB. Please accept our sincere apologies for this error.
In this PSUR (01/01/1999 – 31/12/2003), the CCDS was updated in order to include the following adverse events in section 4.8: Pneumonia, Stevens Johnson syndrome, bronchospasme and irritability.
The decision to add the adverse event "pancreatitis" in the CCDS/SPC has to be discussed and assessed internally. The final decision will be taken end of April. At that time we will communicate you the decision, with an updated SPC if decision is to add pancreatitis, or with a justification if decision is to not add pancreatitis. Please find enclosed the above-mentioned PSUR

**Assessor's comment: Issue not resolved**

**Previous MEB comment:**
In addition, in our letter of the 9th April 2003 you were requested to closely monitor syncope, SIDS and cough following vaccination with MMR II and review this in the next PSUR. This has not been done. Therefore, cumulative review of syncope, SIDS and cough following vaccination with MMR II is requested.

**Answer of the MAH:**
The request was done in the PSUR covering 01/01/1999-31/12/2003. Please find this PSUR enclosed. It contains cumulative review of syncope, SIDS and cough as requested in 2003. Additional data from January 2004 to December 2006 are also enclosed in an additional document.

**Assessor's comment: This is accepted**

**Previous MEB comment:**
The next 3 year PSUR should cover the period 01 Jan 2006 – 31 Dec 2008 and should be submitted within 60 days following data-lock point, unless safety issues require earlier submission.
Due to new legislation the MAH should be aware that the PSUR synchronization project of the PhVWP may require a new PSUR schedule.

**Answer of the MAH:**
In a near future, our product M-M-R II will be replaced by M-M-RvaxPro. This new Measles-Mumps and Rubella vaccine contains recombinant albumin is stead of human albumin. M-M-RvaxPro was registered in centralised procedure on 5 May 2006 under MA number EU/1/06/337/001→013
In order to facilitate the handling of M-M-R II vs. M-M-RvaxPro, we would like to harmonize the PSURs submission, one PSUR will be generated according to ICH E2C recommendations for M-M-R II and M-M-RvaxPro. The data lock point for M-M-R II PSURs is established as the date on which marketing authorization is granted in the EU for M-M-RvaxPro. The EBD of M-M-RvaxPro is 05.05.06 and thus the

[redacted]

covering period was for the 1st 6-month PSUR 05.05.06–04.11.06. (Submitted on 12 Jan 2007 with our request to maintain the Marketing Authorisation) For purposes of the PSUR, a global, descriptive analysis will be performed for all reports combined for M-M-R II, whether or not there is a batch/lot number to identify either M-M-R II or M-M-RvaxPro. Additionally, a descriptive presentation of the data by albumin status will be done for the first four PSURs after licensing. This will allow a review of adverse experiences by batch/lot (HSA, rHA and unknown) while the transition from M-M-R II to M-M-RvaxPro occurs.

The common PSUR will be submitted to you according to the cycle of M-M-RvaxPro and in the scope of the M-M-RvaxPro PSUR submission. It will avoid also that you receive twice the same PSUR.
Next PSUR will cover 05.11.2006 to 04.05.2007

**Assessor's comment: Issue not resolved, see also comment below**

**Previous MEB comment:**
For your information: the information concerning human albumin can not be updated to recombinant human albumin since this PSUR concerns safety information about MMR II and not M-M-RvaxPRO. Therefore, human albumin specific issues (i.e. the warning concerning Creutzfeldt Jacob Disease) cannot be deleted from the CCDS.

**Answer of the MAH:**
Please note that, contrary to CCDS which is an internal document, the paragraph related to Creutzfeldt Jacob Disease will be kept in Dutch SPC of M-M-R II.

**Assessor's comment: This is accepted**

**Previous MEB comment:**
It should be noted that the SPC is not in line with the SPC guideline of October 2005

**Answer of the MAH:**
In parallel to this answer document, please find an application for a Type II variation to modify SPC and PIL for M-M-R II. Please note that in order to harmonize information for M-M-R II in European countries, and also between M-M-R II and M-M-RvaxPRO, this new proposed SPC is based on the CCDS and on the current SPC of M-M-RvaxPRO.

**Assessor's comment:**
Harmonisation of PSUR submission of M-M-R II and M-M-RvaxPro is not acceptable as these products are registered via the national and central procedures respectively. As M-M-RII contains human albumin, it can be anticipated that reactogenicity is different from M-M-RvaxPro that contains recombinant albumin. Therefore, as long as the MAH did not yet replace M-M-RII with M-M-RvaxPro, separate PSURs should be submitted.

Considering the fact that the MAH has submitted an application for harmonisation of the SPC of M-M-R-II with the SPC of M-M-RvaxPro, it should be noted that: 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). 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.

[redacted]