CBG MEB

Casenr: 20607603017 and 20708823020

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X Nationale procedure
O Wederzijdse erkenning
O Decentrale procedure
O Centrale procedure
Europees nummer:

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 FT4: [redacted]
Peer review [redacted]

Date: 07 August 2007

COLLEGE
TER BEOORDELING VAN
GENEESMIDDELEN

CBG MEB

MEDICINES
EVALUATION
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Product name	: MMRII	**RVG NR**	: 17672, 18676
Pharmaceutical form	: Poeder voor injectievloeistof	**ATC**	:
Active constituent	: RUBELLA VIRUS, LEVEND > 1000.0 TCID50/flacon BOFVIRUS, LEVEND > 5000.0 TCID50/flacon MAZELENVIRUS, LEVEND > 1000.0 TCID50/flacon	**PSUR**	: response to PSUR
MAH	: Sanofi Pasteur MSD	**BirthDate**	:
CMS	:	**MRP reference no.**	:

Introduction

The MAH submitted a response regarding the assessment of the MEB concerning the following issues:

☞ **Harmonisation of the PSURS**

Previous MEB 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.

Response MAH:

Although M-M-R™II and M-M-RvaxPro® are registered through national and centralised procedures respectively, the rationale for a single PSUR for M-M-R™II and M-M-RvaxPro® is provided hereafter. M-M-R™II, measles, mumps, and rubella live vaccine has been nationally registered and marketed in countries around the world since 1978. M-M-R™II is currently manufactured using pooled serum derived human serum albumin (HSA) as a component of the viral growth media in the bulk manufacturing process and as a component of the bulk diluents at formulation of the final product.
To address ongoing safety and sourcing concerns related to human blood-derived products, [redacted] planned to substitute rHA (recombinant human albumin) for HSA in the bulk manufacturing process of M-M-R™II.

[redacted]

To comply with EU regulations, a complete new registration through Centralised Procedure (CP) was made due to the recombinant characteristics of rHA. The EC Decision of M-M-RvaxPro® (measles, mumps, and rubella virus vaccine live, MSD manufactured with rHA) was granted on 05-May-2006. In all other countries except EU countries, a variation has been submitted to switch from M-M-R™II HSA to M-M-RII™ rHA and, the rHA-containing vaccine retains thus the same trade name, M-M-R™II. This is not the case in the European Union (E.U.) where the rHA-containing product is referred to as M-M-RvaxPro®.

According to the different international regulations, PSURs are produced with a periodicity that is designed to address multiple international reporting requirements. The PSUR schedule is based upon the International Birth Date (IBD). For both M-M-R™II HSA and M-M-RII™ rHA, one PSUR is generated according to ICHE2C recommendations. Based on the original International Birthdate (01-Apr-1978) for measles, mumps, and rubella virus vaccine live, MSD, PSURs would be prepared on a 5-year basis. However, as mentioned in the Annex to ICH E2C, for products in a long-term PSUR cycle such as M-M-R™II, the return to 6-monthly reporting applies when a new formulation is implemented. Therefore, due to the new registration of M-M-RvaxPro ® under the CP in the EU, the PSUR periodicity for M-M-R™II has been reset to every 6 months, with a data lock point established as the date on which marketing authorization was granted in the EU for M-M-RvaxPro ®: 05 May 2006.
Therefore the first PSUR had a period from 5-May-2006 to 4-Nov-2006. The second 6-month PSUR, which is going to be submitted, covers the period from 05-Nov-2006 to 04-May-2007.

The present circumstance presents a challenge to the routine surveillance procedures which has prompted the development of a Postmarketing Safety Surveillance Analysis. It is expected that, for up to at least the first six months following market introduction of M-M-R™II rHA in both the U.S. and France/Germany, while the number of doses of M-M-R™II rHA released into distributions channels will be known, it will not be possible to know with precision the relative number of doses of M-M-R™ HSA and M-M-R™ rHA actually used in practice. Thus, it will not be possible to determine with precision what the relative adverse event reporting rates are for M-M-R™II HSA and M-M-R™II rHA separately. Without accurate adverse event reporting rates, it will not be possible to determine whether or not any change in the reporting rate for M-M-R™II rHA represents a true signal in need of further analysis or a false signal. Therefore, a Postmarketing Safety Surveillance Analysis employing quantitative methods has been proposed and will be implemented. For purposes of the PSUR, a global, descriptive analysis is 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 HSA or M-M-R™II rHA. Additionally, a descriptive presentation of the data by albumin status is done for the first four PSURs after licensing and/or EU launch. This allows a review of adverse experiences by batch/lot (HSA, rHA and unknown) while the transition from M-M-R™II HSA to M-M-R™II rHA occurs.
In addition, a descriptive presentation of EU reports by vaccine name will also be conducted during the first 4 PSURs after EU launch. This includes a description of the patient population (e.g. age, gender, past medical history, concomitant medications), the serious/non serious criteria of the adverse experience and importantly the time to onset of the adverse experience temporally associated with the administration of the vaccine. Together with medical judgment, a descriptive epidemiologic presentation of the EU data assists in determining the assessment of association of the adverse experience with the vaccine. Up to now, M-M-RvaxPro® is not yet launched in Europe and such descriptive presentation of EU reports has not yet been carried out.

Considering all the circumstances presented above, it is reasonable and appropriate to provide a single PSUR for M-M-R™II and M-M-RvaxPro®.

Assessor's comment: Taking into account that the PSUR cycle is amended, this can be accepted. However, it is anticipated that the MAH will distinguish into separate sections for M-M-R™II and M-M-RvaxPro® within 1 single PSUR.

☞ **SmPC**

Previous MEB Comment:

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Harmonisation of the SPC with the SmPC as approved for M-M-RvaxPro is accepted provided that you will still consider Toxic Epidermal Necrolysis (TEN) and pancreatitis to be included in the SPC for the M-M-RII.

Response MAH:

The manufacturer [redacted] is not in favor 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™II 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. [redacted] will continue monitor all reports of TENS, should we receive them, at adverse experience reporting meetings (AERTs).

Assessor's comment: Provided that the MAH will continue close monitoring and will provide cumulative reviews in all upcoming PSURs, this is accepted.

A new proposed SPC, updated with 'pancreatitis'in section 4.8 was enclosed.

Assessor's comment: issue partly resolved, because the MAH regretfully has translated pancreatitis in 'alvleesklierontsteking'. The Dutch MedDRA term for pancreatitis remains 'pancreatitis'. Please include pancreatitis instead of 'alvleesklieronsteking'.

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