20 February 2013
EMA/78481/2013
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## M-M-RVAXPRO

Measles, mumps and rubella vaccine (live)

**Procedure no:** EMEA/H/C/000622/A-20/0045

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Background information on the procedure

On the basis of the most recent published data on rubella containing vaccines, in particular for pregnant women it was considered justified to review whether all monovalent and multivalent measles, mumps, rubella and varicella (MMRV) vaccines should remain contraindicated in pregnant women as vaccination in some individual cases may outweigh the risk.

Published data also indicated that other groups of subjects than pregnant women could benefit from a MMRV vaccine (e.g. patients with deficiency or specific pneumococcal antibody deficiency) and therefore the contraindication for immunocompromised individuals needed to be reviewed.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 15 March 2012 to assess the above concerns and its impact on the benefit/risk for M-M-RVAXPRO, and to give its opinion on measures necessary to ensure the safe and effective use of M-M-RVAXPRO, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

# 2. Scientific discussion

M-M-RVAXPRO is a trivalent vaccine containing the components of measles, mumps and rubella live attenuated viruses. M-M-RVAXPRO has been authorised by the European Commission for simultaneous vaccination against measles, mumps and rubella in individuals from 12 months of age since May 2006.

On the basis of the most recent published data on rubella containing vaccines, in particular when inadvertently administrated to pregnant women, it was considered justified to review whether M-M-RVAXPRO should remain contraindicated in pregnant women as vaccination in some individual cases may outweigh the risk.

In addition, published data also indicated that some groups of individuals other than pregnant women could benefit from a MMRV vaccine and therefore the contraindication for immunocompromised subjects needed to be reviewed.

Evidence from post marketing surveillance and published literature that focused on risk of spontaneous abortion, miscarriage, stillbirth, immaturity and low birth weight in women susceptible to measles, mumps and/or rubella and risk of malformation and congenital rubella syndrome (CRS) in offspring of such women were considered for the review of the contraindication on pregnancy.

Regarding the contraindication on immunocompromised subjects, an assessment of the experience with MMR vaccines concerning safety in subjects with various types of immune deficiencies (e.g. T-cell defects, sub-class deficiencies etc.) was provided.

Relevant data is discussed below.

## *2.1. Clinical aspects*

### 2.1.1. Measles, mumps and rubella containing vaccines in pregnancy

Vaccination against measles, mumps and rubella is contraindicated in pregnant women. Therefore, only limited data are available on spontaneous abortion, malformations or CRS of women vaccinated with MMR vaccines.

Data from post marketing surveillance and published literature regarding MMR vaccines were considered by the CHMP.

Post-marketing database identified 971 individual case safety reports (ICSRs) for MMR vaccines and 78 (ICSRs) for monovalent rubella vaccines in women who were pregnant when vaccinated with these vaccines. No case of CRS has been identified and the number of congenital malformations or spontaneous abortions did not indicate a safety concern related to the inadvertent vaccination with MMR vaccines during pregnancy. In addition, three retrospective cases from spontaneous reporting in which congenital anomalies were reported in liveborn and where one case had characteristic of CRS were provided. However, the cases were also poorly documented. The frequency of spontaneous abortion and congenital anomalies reported was as expected for pregnant women that have not been vaccinated.

The CHMP considered that mumps virus has been shown to infect the placenta and foetus, although there is no evidence that mumps vaccines can cause congenital malformations in humans (Plotkin et al. 2008[1]). In contrast to rubella and mumps virus, measles virus does not cross the placenta and therefore does not infect the foetus.

The incidence of CRS following inadvertent vaccination of pregnant women has been evaluated through rubella registries in the U.S. and Europe and through surveillance for cases during more recent mass vaccination campaigns. A total of 680 live births to rubella-susceptible women were evaluated. It was shown that none of the infants was found to have CRS. Based on these data a maximum theoretical risk for CRS of 0.5% for infants born to mothers vaccinated within three months of pregnancy was found, and a maximum theoretical risk of 1.3% for infants born to mothers vaccinated within the first 20 weeks of pregnancy (Morice et al. 2009[2]). The overall estimated theoretical risk of severe malformations attributed to the vaccine strain against rubella varies between 0 and 1.6% (Bozzo et al. 2011[3]; Watson et al. 1998[4]).

Further data are available from surveillance of a mass vaccinations campaign between 2001 and 2008 for rubella and congenital rubella syndrome elimination in the Americas (Castillo et al.[5]). More than 2000 pregnant women were followed-up and classified as susceptible at the time of vaccination. During this campaign, no case of CRS due to the vaccine strain was diagnosed.

When considering the data from studies in the literature and the data from post-marketing surveillance the CHMP concluded that although a theoretical risk cannot be excluded, no cases of CRS have been reported in more than 3500 susceptible women who were unknowingly in early stages of pregnancy when vaccinated against rubella.

Because of this theoretical teratogenic risk, the World Health Organisation (WHO) recommended in 2011 that vaccination against rubella should be avoided in principle, in pregnant women and women who intend to become pregnant should be advised to delay for 1 month following rubella vaccination[6].

[1] Plotkin SA, Orenstein WA and Offit PA. Mumps vaccine. Vaccines 2008;435-65
[2] Morice A, Ulloa-Gutierrez R, and Avila-Agüero ML. Congenital rubella syndrome: progress and future challenges. Expert Rev Vaccines. 2009 Mar;8(3):323-31
[3] Bozzo P, Narducci A, and Einarson A. Vaccination during pregnancy. Can Fam Physician. 2011 May;57(5):555-7
[4] Watson JC, Hadler SC, Dykewicz CA, et al. Measles, mumps, and rubella vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1998 May 22;47(RR-8):1-57

[5] Castillo-Solorzano C, Reef SE, Morice A et al. Rubella vaccination of unknowingly pregnant women during mass campaigns for rubella and congenital rubella syndrome elimination, the Americas 2001-2008. J Infect Dis 2011;204 Suppl 2:S713-7

[6] World Health Organization. Rubella vaccines: WHO position paper.301-316.15-7-2011. Available on http://www.who.int/wer/2011/wer8629.pdf 29(86) Ref Type: Internet Communication

Current data indicate that rubella IgM after vaccination peaks around 30 days after vaccination and IgG is also detectable.

Having considered all available data, the CHMP is of the opinion that M-M-RVAXPRO should continue to be contraindicated in pregnant women. Taking into account that rubella vaccination induces a fast immune response that make post-exposure prophylaxis possible, based on available evidence and as reflected in WHO recommendation, the CHMP considered that there are sufficient data to reduce the period post-vaccination where pregnancy should be avoided. The product information is therefore amended accordingly to reflect that pregnancy should be avoided for 1 month following vaccination instead of 3 months. For completeness, the product information was updated to reflect the most recent published data regarding vaccination against rubella in pregnant women. Based on the low theoretical teratogenic risk and the fact that no case of CRS has been reported, it should be also mentioned in the SmPC that inadvertent vaccination of unknowingly pregnant women with M-M-RVAXPRO should not be a reason for termination of pregnancy.

### 2.1.2. Measles, mumps and rubella containing vaccines in immunocompromised individuals

Vaccination of immunocompromised individuals with live attenuated viral MMR vaccines is generally contraindicated, however some subjects may benefit from vaccination.

Based on evidence available from clinical trials and post marketing safety surveillance, the CHMP acknowledged that M-M-RVAXPRO should remain contraindicated in subjects with severely impaired humoral and/or cellular immune systems such as severe combined immunodeficiency (SCID) and agammaglobulinemia. However, individuals with selected or non-specific immune deficiencies such as isolated IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases might benefit from vaccination. Data from literature (Moss W and Lederman H. 1998[7]) indicated that these immunocompromised subjects do not appear to be at higher risk of complications than the general populations. Moreover, most national immunisation committees and expert groups recommend that children with minor immune deficiencies should receive MMR vaccination.

The CHMP agreed that patients with various IgG subclass deficiencies are not able to develop an appropriate antibody response to vaccines including MMR vaccines and therefore, there is a risk of serious adverse events from the use of lives attenuated viral vaccines in this group of patients. The contraindication should remain in this specific subpopulation.

Because wild-type measles can result in severe disease in HIV-infected children vaccination is especially important for HIV-infected children. Severely immunocompromised HIV infected children and adults should not receive M-M-RVAXPRO, however there is sufficient evidence that MMR vaccinations are safe for HIV-infected persons who have mild and moderate clinical disease and adequate CD4 counts. Therefore, the CHMP proposed a modification of the existing contraindication to specify that for HIV, the WHO classification of HIV-related disease in adults and children published in 2006 should be applied as follows :

“Immunological criteria for diagnosing advanced HIV in a child younger than five years of age with severe HIV infection:

%CD4+ <25 among those younger than 12 months

%CD4+ <20 among those aged 12–35 months

[7] Moss W, Lederman H. Immunization of the immunocompromised host. Clin Focus Primary Immune Defic. 1998;1:1-8

%CD4+ <15 among those aged 36–59 months"

Therefore, in children with severe HIV infection vaccination is contraindicated. As indicated above, in individuals with selected immune deficiencies (e.g. IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases) vaccination may be considered, if the benefit outweighs the risk of vaccination.

In view of the above, the CHMP concludes that the current contraindication for use of M-M-RVAXPRO in immunocompromised subjects should be amended to clarify that, according to WHO guidelines and scientific data, for HIV-infected patients age specific %CD4+ is to be included. Moreover, a warning should be added as vaccination may be considered in subjects with selected immune deficiencies (e.g. IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases), if the benefit outweighs the risk of vaccination.

## *2.2. Product information*

The CHMP recommended the following amendments to be introduced in the summary of product characteristics (SmPC) and package leaflets (PL).

**Summary of Product Characteristics**

*Pregnancy*

The section 4.3 (Contraindications) and section 4.6 (Fertility, pregnancy and lactation) of the SmPC should be amended in order to reflect that pregnancy should be avoided for 1 month following vaccination instead of 3 months.

The section 4.6 should also reflect that inadvertent vaccination of unknowingly pregnant women with M-M-RVAXPRO should not be a reason for termination of pregnancy. It should also be mentioned that even if a theoretical risk cannot be excluded no cases of congenital rubella syndrome have been reported in more than 35000 susceptible women who were unknowingly in early stages of pregnancy when vaccinated with rubella containing vaccines.

*Immunocompromised individuals*

The section 4.3 should also reflect that vaccination with M-M-RVAXPRO is contraindicated in subjects with severe humoral or cellular (primary or acquired) immunodeficiency and for HIV-infected patients an age specific %CD4+ is to be included.

The section 4.4 should reflect that vaccination may be considered in patients with selected immune deficiencies (e.g. IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases), if the benefit outweighs the risk of vaccination.

Note: The telephone number of the local representative in Malta has been updated.

**Package Leaflet**

In line with the recommendation made in the SmPC, the section "Do not use" and "Pregnancy and breastfeeding" should be amended in order to reflect that pregnancy should be avoided for 1 month following vaccination instead of 3 months.

# 3. Overall discussion and benefit/risk assessment

M-M-RVAXPRO is a trivalent vaccine which is indicated in vaccination of individuals from 12 months of age against measles, mumps and rubella viruses. Vaccination with M-M-RVAXPRO is contraindicated in pregnant women and in immunocompromised subjects.

The CHMP reviewed all available evidence regarding these specific populations, notably data from post-marketing surveillance including data from a pregnancy registry, published literature and available guidance, such as the WHO recommendation.

Regarding vaccination in pregnant women, it was noted that M-M-RVAXPRO is contraindicated in pregnant women and therefore only limited data of spontaneous abortion, malformations, congenital rubella syndrome (CRS) following vaccination were available. Evidence of transplacental transmission of mumps and rubella wild-type virus is known, however measles viruses do not cross the placenta and therefore do not infect the fetus. The evidence to date does not indicate a safety concern with respect to spontaneous abortion or congenital malformations related to the inadvertent administration of MMR vaccines in pregnant women. In addition, no cases of CRS have been reported in post-marketing surveillance or in published literature. However, it was noted by the CHMP that follow-up data of children of pregnant mothers exposed to monovalent or multivalent MMR vaccines virus were lacking and were too poorly documented to draw any conclusion.

The CHMP considers that an estimated theoretical risk of CRS cannot be ruled out. It was also noted that available guidance, such as WHO recommendations, takes into account this theoretical teratogenic risk and states that rubella containing vaccines should be avoided in principle in pregnant women.

The CHMP concluded that the contraindication of M-M-RVAXPRO in pregnant women remains. However, the CHMP considered that there are sufficient data to amend the product information and reflect that pregnancy should be avoided for 1 month following vaccination instead of 3 months, in line with current WHO recommendations. In addition, the product information should reflect the most recent published data regarding inadvertent vaccination against rubella in pregnant women.

Regarding vaccination of immunocompromised subjects with M-M-RVAXPRO the CHMP considered that although this vaccine should continue to be contraindicated, some individuals may benefit from vaccination.

The CHMP acknowledged that M-M-RVAXPRO should remain contraindicated in patients with severely impaired humoral or cellular immune systems such as severe combined immunodeficiency (SCID) and agammaglobulinemia. However, the CHMP concludes that the current contraindication for use of M-M-RVAXPRO in immunocompromised subjects should be amended to clarify that, according to WHO guidelines and scientific data, for HIV-infected patients age specific %CD4+ is to be included. Moreover, a warning should be added as vaccination may be considered in patients with selected immune deficiencies (e.g. IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases), if the benefit outweighs the risk of vaccination.

# 4. Overall conclusion

Having considered the overall submitted data provided by the MAH, the CHMP concluded that M-M-RVAXPRO should remain contraindicated during pregnancy. However, the CHMP was of the opinion that the current data were sufficient to amend the product information in order to reflect that pregnancy should be avoided for 1 month following vaccination with M-M-RVAXPRO and to reflect the most recent published data on rubella vaccination in pregnancy.

With regard to the immunocompromised patients, the CHMP concluded that in view of the available data vaccination with M-M-RVAXPRO should continue to be contraindicated in severely impaired humoral and/or cellular immune systems such as severe combined immunodeficiency (SCID) and hypogammaglobulinemia, however, vaccination may be considered in patients with selected immune deficiencies when the benefit outweighs the risk of vaccination.

The CHMP recommended the amendment to the terms of the marketing authorisation for M-M-RVAXPRO for which the revised summary of product characteristics and package leaflet are set out respectively in annexes I and IIIB of the opinion.

The scientific conclusions and the grounds for the amendment of the SmPC, Annex II and package leaflet are set out in Annex II of the opinion.

# 5. Conclusion and grounds for the recommendation

Whereas

- the CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004, for M-M-RVAXPRO initiated by the European Commission.
- the CHMP reviewed all available data regarding use in pregnant women and in immunocompromised patients of rubella containing vaccines, including the most recent publications and data from post-marketing surveillance for monovalent and multivalent measles, mumps and rubella vaccines.

The CHMP concluded

- that the data provided were too limited and poorly documented to draw any conclusion and therefore without any sufficient data M-M-RVAXPRO should remain contraindicated during pregnancy.
- that the data were sufficient to amend the product information to mention that pregnancy should be avoided for 1 month (instead of 3 months) following vaccination. The CHMP also considered that the most recent published data regarding vaccination against rubella in pregnant women should be reflected in the summary of product characteristics.
- that vaccination with M-M-RVAXPRO vaccines may be considered in patients with selected immune deficiencies when the benefit outweighs the risk of vaccination. The contraindication in this patient population was also further defined by inclusion of age specific %CD4+ for HIV-infected patients.

The CHMP has therefore recommended the variation to the terms of the marketing authorisation for M-M-RVAXPRO in accordance to the Product Information set out in annexes I, II and IIIB.

The divergent positions are appended to this report.

# Appendix

## *Divergent positions*

## Review under Article 20 of Regulation (EC) No 726/2004

Procedure number: EMEA/H/C/000604/A-20/0045

M-M-RVAXPRO (Measles, mumps and rubella vaccine (live))

**Divergent statement**

In general, the use of MMRV vaccines should be avoided during pregnancy. However, following the guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling, the absolute contra-indication for pregnancy could be changed.

This guideline describes that if there are enough data showing no harm during pregnancy, the wording in the SPC should be adapted.

For rubella containing vaccines which have the highest theoretical risk on congenital syndromes no cases of congenital rubella syndrome (CRS) have been reported in the literature. More than 3500 children born out of rubella sero-negative mothers that were inadvertently vaccinated during the pregnancy are reported without having the CRS.

Therefore a minority of the CHMP members proposes to downgrade the absolute contraindication for pregnancy to another warning.

For varicella containing vaccines the contraindication still holds.

**CHMP members expressing a divergent opinion:**

| | | |
|---|---|---|
| Pieter Neels (BE) | 13 December 2012 | Signature: ..... |
| Jens Heisterberg (DK) | 13 December 2012 | Signature: ..... |
| Pierre Demolis (FR) | 13 December 2012 | Signature: ..... |
| Jacqueline Genoux-Hames (LU) | 13 December 2012 | Signature: ..... |
| Juris Pokrotnieks (LV) | 13 December 2012 | Signature: ..... |

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**CHMP member expressing a divergent opinion:**

| | | |
|---|---|---|
| Jacqueline Genoux-Hames (LU) | 13 December 2012 | Signature: …… |

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**CHMP member expressing a divergent opinion:**

| | | |
|---|---|---|
| Karsten Bruins Slot (NO) | 13 December 2012 | Signature: …… |