EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/77344/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Monovalent and multivalent measles, mumps, rubella and varicella vaccines

Common name: Monovalent and multivalent measles, mumps, rubella and varicella vaccines (live)

Procedure No: EMEA/H/A-31/1333

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

1.1. Referral of the matter to the CHMP

On the basis of the most recent published data on rubella containing vaccines, in particular when administrated to pregnant women, Belgium national competent authorities 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 indicated also 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 also to be reviewed.

In view of the above, Belgium national competent authorities considered of Community interest to review the benefit/risk of monovalent and multivalent MMRV vaccines in the above mentioned populations (i.e. pregnant women and subjects with immune deficiencies).

On 9 March 2012, Belgium national competent authorities triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing monovalent and multivalent measles, mumps, rubella and varicella vaccines should be maintained or varied.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

Monovalent and multivalent measles, mumps, rubella and/or varicella containing vaccines are live attenuated vaccines. They are indicated in vaccination of adults and children against these viruses. Vaccination with these MMRV vaccines is contraindicated in pregnant women and in immunocompromised subjects.

On the basis of the most recent published data on rubella containing vaccines, in particular when inadvertently administrated to pregnant women, Belgium national competent authorities considered justified to review whether monovalent and multivalent MMRV vaccines 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, rubella and/or varicella, risk of malformation and congenital rubella syndrome (CRS) in offspring of such women, and risk of congenital varicella syndrome (CVS) were considered for the review of the contraindication on pregnancy.

Regarding the contraindication on immunocompromised subjects, an assessment of the experience with MMRV 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.

2.2. Clinical aspects

2.2.1. 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 and congenital rubella syndrome in the offspring of women vaccinated with MMR vaccines. Data from post-marketing surveillance including spontaneous reports and pregnancy registry indicated that approximately 400 women were inadvertently vaccinated with a multivalent MMR vaccine or a monovalent rubella containing vaccine. The frequency of spontaneous abortion and congenital anomalies reported was as expected for pregnant women that have not been vaccinated. In addition, no case of congenital rubella syndrome (CRS) was observed.

It was noted by the CHMP that the cases reported were poorly documented.

The data from post-marketing surveillance including spontaneous reports and pregnancy registry provided by the MAHs regarding monovalent or multivalent measles, mumps and rubella vaccines were also too limited to draw any conclusion.

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.[1]). 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.

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[2]). In contrast to rubella and mumps virus, measles virus does not cross the placenta and therefore does not infect the foetus. Regarding rubella containing vaccines, two cases (one reported in the literature and one post-marketing) of possible trans-placental rubella vaccine virus strain transmission to the foetus were reported. One case of a persistent foetal rubella vaccine virus infection was also reported in the literature, without development of any discernible adverse effect after inadvertent rubella vaccination during early pregnancy. However, the cases were also poorly documented.

When considering the data from studies in the literature and the data 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.

Despite the scientific literature not reporting a real risk of CRS after rubella vaccination during pregnancy, a theoretical risk of 0.5% has been estimated if the vaccine is administrated during the first trimester and a maximum of 1.3% if applied between 1-2 weeks before and 4-6 weeks after conception (Morice et al. 2009[3]). The overall estimated theoretical risk of severe malformations attributed to the vaccine strain (Wistar RA 27/3) against rubella varies between 0 and 1.6% (Bozzo et al. 2011[4]; Watson et al. 1998[5]).

Because of this theoretical teratogenic risk, the World Health Organization (WHO) recommended in 2011 that vaccination against rubella should be avoided in principle, in pregnant women and women who

[1] 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
[2] Plotkin SA, Orenstein WA and Offit PA. Mumps vaccine. Vaccines 2008;435-65
[3] 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
[4] Bozzo P, Narducci A, and Einarson A. Vaccination during pregnancy. Can Fam Physician. 2011 May;57(5):555-7
[5] 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

intend to become pregnant should be advised to delay for 1 month following rubella vaccination[6]. 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 concluded that MMR vaccination 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[6], 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 monovalent or multivalent mumps, measles and rubella containing vaccines should not be a reason for termination of pregnancy.

2.2.2. Measles, mumps, rubella and varicella containing vaccines in pregnancy

Varicella is caused by varicella-zoster virus (VZV), a herpes virus. Pregnant women who are infected with wild type varicella may develop serious complications as pneumonia or exitus. Although varicella infection is not known to cause spontaneous abortion or stillbirth it can still be associated with preterm delivery. In addition, congenital varicella syndrome (CVS) may occur in infants born to women who experience varicella disease following infection with wild-type VZV during pregnancy. The risk of CVS is estimated to be approximately 0.4% when maternal infection occurs from conception through to the 12th week of gestation, and 2% when infection occurs between the 13th and 20th week of gestation.

Vaccination against varicella is contraindicated in pregnant women. Therefore, as for the MMR vaccines, only limited data are available on inadvertent exposure of pregnant women. Data from post marketing surveillance was submitted for these vaccines.

Data available from subjects exposed to a monovalent containing varicella live attenuated virus vaccine prior or during pregnancy showed outcomes in 115 women. It was observed that 81 (70%) children born of women vaccinated with a varicella vaccine were live births including one infant with congenital abnormalities and of the 34 (30%) non-live birth pregnancies, the majority was electively terminated or were spontaneous abortions (20, i.e. 17%). The frequency of spontaneous abortion and congenital anomalies reported were as expected for pregnant women that have not been vaccinated. In addition, no case of CVS was reported and no information on foetal vaccine virus transmission was present.

Further data did not indicated a safety concern with respect to spontaneous abortion, miscarriage, stillbirth, immaturity, low birth weight or congenital malformation related to inadvertent administration of MMRV vaccines to pregnant women. Prospective reports on 773 pregnancies from a varicella-zoster virus (VZV)-pregnancy registry and on 966 pregnancies from spontaneous reports have shown respectively 78 and 94 spontaneous abortions, 18 and 37 congenital anomalies. Retrospective reports on 93 pregnancies mention 21 spontaneous abortions (23%) and 12 anomalies (13%). However, it was noted that several cases were poorly documented. Of note, the data seemed to show that there was no difference in pregnancy outcome between seronegative and seropositive women. In addition, no cases of CVS were detected over the 15 years that the VZV registry has been in place. The risk of CVS following vaccination with varicella live attenuated virus vaccine is a theoretical risk, however, considering the limited data and

[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

that the cases were poorly documented the CHMP considered that it was not possible to draw any conclusion.

The CHMP concluded that the data available are insufficient to determine the actual risk to the foetus when vaccinating seronegative women with live attenuated virus vaccines. Having considered all available data and although the data from the VZV-pregnancy registry and spontaneous reports did not show evidence of CVS in pregnant women inadvertently vaccinated with a varicella containing vaccine, the data were too limited, not well documented, to support any changes to the current contraindication in pregnant women.

Therefore, the CHMP concluded that varicella vaccination should continue to be contraindicated in pregnant women.

Taken into account that varicella vaccination induces a fast immune response that makes post-exposure prophylaxis possible, based on available evidence and as reflected in WHO recommendation[7] 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 to reflect that pregnancy should be avoided for 1 month following vaccination instead of 3 months

2.2.3. Measles, mumps, rubella and varicella vaccines in immunocompromised individuals

Vaccination of immunocompromised individuals with live attenuated viral MMRV vaccines is contraindicated, however some subjects may benefit from vaccination and this is reflected in the product information of these vaccines.

Based on evidence available from clinical trials and post marketing safety surveillance, the CHMP acknowledged that MMRV vaccines 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[8]) indicated that these immunocompromised subjects do not appear to be at higher risk of complications than the general population. Moreover, most national immunisation committees and expert groups recommend that children with selected immune deficiencies should receive MMRV vaccination.

The CHMP also reviewed specifically the subpopulation of patients having various IgG subclass deficiencies and concluded that they are not able to develop an appropriate antibody response to vaccines including MMRV vaccines and that there is a risk of serious adverse events from the use of lives attenuated viral vaccines in this group of patients. The CHMP therefore concluded that 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 MMRV vaccines, however there is sufficient evidence that MMRV 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 :

[7] World Health Organization. Varicella vaccines: WHO position paper.1998;73:241-248.Available on http://www.who.int/immunization/wer7332varicella_Aug98_position_paper.pdf Ref Type: Internet Communication
[8] Moss W, Lederman H. Immunization of the immunocompromised host. Clin Focus Primary Immune Defic. 1998;1:1-8

"*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

%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 MMRV vaccines 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 outweigh the risk of vaccination.

2.3. Overall benefit/risk assessment

Monovalent and multivalent measles, mumps, rubella and/or varicella containing vaccines are live attenuated vaccines which are indicated in vaccination of adults and children against these viruses. Vaccination with these MMRV vaccines 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 MMRV vaccines are contraindicated in pregnant women and therefore only limited data of spontaneous abortion, malformations, congenital rubella or varicella syndrome (CRS or CVS) following vaccination were available. Evidence of transplacental transmission of mumps, rubella and varicella 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 MMRV vaccines in pregnant women. In addition, no cases of CRS or CVS 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 MMRV vaccines virus were lacking and were too poorly documented to draw any conclusion.

The CHMP considers that an estimated theoretical risk of CRS or CRV 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 WHO recommendations for varicella containing vaccines also states that due to theoretical risk to the fetus, pregnancy should be avoided.

The CHMP concluded that the contraindication of MMRV vaccines 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 MMRV live attenuated viral vaccines, the CHMP considered that although these vaccines should continue to be contraindicated, some individuals may benefit from vaccination.

The CHMP acknowledged that MMRV vaccines 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 MMRV vaccines 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.

2.4. Changes to the 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 (SmPC)

Pregnancy

For monovalent and multivalent measles, mumps, rubella and varicella containing vaccines, 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 wording on pregnancy in section 4.4 (Special warnings and precautions for use) should be deleted.

The section 4.6 should also reflect that inadvertent vaccination of unknowingly pregnant women with monovalent or multivalent measles, mumps and rubella containing vaccines should not be a reason for termination of pregnancy. It should also be mentioned for rubella containing vaccines that even if a theoretical risk cannot be excluded no cases of congenital rubella syndrome have been reported in more than 3500 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 MMRV vaccines 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.

Package leaflet (PL)

Pregnancy

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. In addition, for monovalent and multivalent MMR vaccines it should be mentioned that in case of inadvertent vaccination of pregnant women, this should not be a

reason for termination of pregnancy. In addition, any wording on pregnancy and breastfeeding should be deleted from the section “Warnings and precautions”.

Immunocompromised individuals

The section “Do not use” should reflect that the vaccine should not be used if an individual has any illness (such as Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS)) or takes any medicine that weakens the immune system.

The section “Warnings and precautions” should reflect that if an individual has a weakened immune system (e.g. such as HIV infection), this individual should be closely monitored as the responses to the vaccines may not be sufficient to ensure a protection against the illness.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs, the CHMP concluded that monovalent and multivalent MMRV vaccines 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 and to reflect the most recent published data on rubella vaccination in pregnancy for monovalent rubella vaccines and multivalent MMR vaccines.

With regard to immunocompromised patients, the CHMP concluded that in view of the available data vaccination with MMRV vaccines should continue to be contraindicated in severely impaired humoral or cellular immune systems such as severe combined immunodeficiency (SCID) and agammaglobulinemia, however, vaccination may be considered in patients with selected immune deficiencies when the benefit outweigh the risk of vaccination. The contraindication in this patient population was also further defined by inclusion of age specific %CD4+ for HIV-infected patients.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion.

The divergent positions are appended to this report.

Appendix

Divergent positions

Article 31 referral of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1333

Monovalent and multivalent measles, mumps, rubella and varicella vaccines

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: .....