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Questions and answers on the review of monovalent and multivalent measles, mumps, rubella and/or varicella vaccines

Outcome of procedures under Article 20 of Regulation (EC) No 726/2004 and Article 31 of Directive 2001/83/EC

On 13 December 2012, the European Medicines Agency completed a review of the use of monovalent and multivalent measles, mumps, rubella and/or varicella vaccines (MMRV) during pregnancy and in patients with immune deficiencies (weakened immune systems).

The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that these vaccines should continue to be avoided during pregnancy, but that inadvertent vaccination of pregnant women with measles-, mumps- and/or rubella-containing vaccines should not be a reason for termination of pregnancy.

In addition MMRV should continue to be avoided in patients with the most severely weakened immune systems, but their use could be considered in less severe immune deficiency. The Committee also recommended that some changes be made to the product information to clarify the risks and precautions to be taken.

What are MMRV?

MMRV are vaccines that help protect against the viral infections measles, mumps, rubella, and varicella (which may cause chickenpox or shingles [zoster]). They contain live attenuated (weakened) versions of the viruses responsible for these diseases. MMRV may be available as individual vaccines for each infection (monovalent) or as combination vaccines (multivalent).

The multivalent vaccines M-M-RVAXPRO and ProQuad, and the monovalent zoster (shingles) vaccine Zostavax, are centrally authorised for use throughout the European Union (EU). Other monovalent and multivalent vaccines against measles, mumps, rubella, and varicella have been available for many years and are authorised by national procedures in the EU Member States, under different trade names including Amunovax, Priorix, Priorix Tetra, Provarivax, R.O.R. Vax, Rouvax, Trivivac, Varilrix, Varivax, and associated names.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Why were MMRV reviewed?

Some viruses are able to cross the placenta in pregnant women and infect their unborn babies. In particular, rubella can cause malformations and problems particularly with the ears, eyes and heart (known as 'congenital rubella syndrome') and varicella can cause malformations affecting the limbs (known as 'congenital varicella syndrome') in babies whose mothers become infected in early pregnancy. MMRV contain weakened but live viruses. Although these are too weak to cause health problems in healthy adults, their use in pregnant women has not been authorised due to a potential risk to the unborn baby, and women have been advised not to become pregnant for three months after vaccination.

MMRV are also contraindicated in patients with immune deficiencies, in whom the vaccine may not work properly and who might be at risk of developing severe or widespread disease.

However, since these vaccines were authorised, new data from post-marketing use and from the published literature have become available on their safety in pregnancy and in patients with immune deficiencies. As a result, the Belgian medicines agency asked the CHMP to carry out an assessment of the benefit-risk balance of vaccination in these groups and to issue an opinion on whether the marketing authorisations for MMRV should be varied or maintained. At the same time, the European Commission asked the CHMP to extend their considerations to cover the centrally authorised products, and examine if their marketing authorisations should be varied or maintained.

Which data has the CHMP reviewed?

The CHMP reviewed the available safety data on MMRV in pregnancy from post-marketing use and the published literature, focusing on the risk of spontaneous abortion, stillbirth, malformations, immaturity and low birth weight. This included reports on over 3,500 women inadvertently given a rubella-containing vaccine in early pregnancy, and over 1,800 who were given a varicella-containing vaccine during pregnancy. The CHMP also considered available guidance from the World Health Organization.

For patients with immune deficiencies, the Committee looked at evidence from clinical studies and reports from post-marketing use.

What are the conclusions of the CHMP?

Although a risk cannot be completely excluded, no cases of congenital rubella syndrome or congenital varicella syndrome have been reported among over 5,300 reports in women who were inadvertently given MMRV during pregnancy. The rate of malformations or spontaneous abortions in women who were exposed to MMRV during pregnancy was no higher than the expected rate in unvaccinated women. However, the evidence, including the follow-up of some of the cases, was not sufficient to allow the Committee to be certain there was no association. The evidence did suggest that there was no need to delay pregnancy for more than one month after vaccination.

Patients with severe immune deficiencies were at risk of serious adverse effects if given live virus vaccines, but in patients with minor immune deficiencies, including those with HIV infection but adequate blood counts of CD4 cells (a type of white blood cell important in fighting infection), the evidence suggested that MMRV could be given safely and might provide benefit.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of MMRV do not outweigh their risks in pregnancy or in severe immune deficiencies, and recommended that vaccination should continue to be contraindicated in these groups. However, women intending to become pregnant need only delay for

one month after vaccination, and inadvertent rubella vaccination of women who are pregnant need not be a reason for termination of the pregnancy. Vaccination may be considered in patients with minor immune deficiencies if the benefit outweighs the risk. (This does not apply to Zostavax, which has different strength and indications.) The product information should be updated to reflect these changes.

The full changes made to the information to doctors and patients are detailed here for M-M-RVAXPRO, here for ProQuad, here for Zostavax and here for the nationally authorised products.

What are the recommendations for patients?

- Women should not be given monovalent or multivalent MMRV during pregnancy. If a woman is, or thinks she may be, pregnant she should tell her doctor or nurse before receiving any of these vaccines.
- Women who are given one of these vaccines should take the necessary precautions to avoid becoming pregnant for one month after vaccination.
- If a woman becomes pregnant within one month after receiving one of these vaccines, it does not mean that her baby is definitely at risk, or that the pregnancy needs to be terminated.
- Patients with severe weakness of their immune system must not receive these vaccines. In patients with less severe immune weakness, vaccination may be considered, although it does not always give the same protection as in a person with a healthy immune system.
- Patients who have any questions should speak to their doctor or pharmacist.

What are the recommendations for prescribers?

- Vaccination with MMRV remains contraindicated in pregnancy and in patients with severe humoral or cellular immunodeficiency (such as severe combined immunodeficiency, agammaglobulinaemia, or AIDS).
- Women should be advised to delay becoming pregnant for one month after MMRV vaccination. Inadvertent vaccination with rubella-containing vaccines during pregnancy is not a reason for termination.
- In children with HIV infection, vaccination is contraindicated in those with age-specific CD4+ percentages of less than 25% below 12 months, less than 20% between 12 and 35 months, or less 15% between 36 and 59 months.
- Vaccination may be considered in patients with certain immune deficiencies where the benefits outweigh the risks of vaccination (e.g. asymptomatic HIV-infected patients, patients with selective IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease and complement deficiency diseases).
- Immunocompromised patients who are vaccinated may not develop adequate immunity and should be monitored for subsequent development of measles, parotitis, rubella or varicella after contact with these diseases.

The European Commission issued a decision for MMRV Article 31 on 28 February 2013.

The European Commission issued a correcting decision for MMRV Art 31 on 27 June 2013.

The European Commission issued a decision for M-M-RVAXPRO Article 20 on 20 February 2013.

The European Commission issued a decision for ProQuad Article 20 on 18 February 2013

The European Commission issued a decision for Zostavax Article 20 on 13 February 2013.

The current European public assessment report for M-M-RVAXPRO can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

The current European public assessment report for ProQuad can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

The current European public assessment report for Zostavax can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports