18 February 2013
EMA/78633/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ProQuad

Measles, mumps, rubella and varicella vaccine (live))

Procedure no: EMEA/H/C/000622/A-20/0060

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 ProQuad, and to give its opinion on measures necessary to ensure the safe and effective use of ProQuad, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

ProQuad is a quadrivalent vaccine containing the components of measles, mumps, rubella and varicella lives attenuated viruses. ProQuad has been authorised by the European Commission for simultaneous vaccination against measles, mumps, rubella, and varicella in individuals from 12 months of age since April 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 ProQuad 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.

2.1. Clinical aspects

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

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

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

Data from the routine pharmacovigilance and enhanced surveillance through the Varicella-Zoster Virus (VZV)-Pregnancy Registry have indicated 5 reports of inadvertent exposure with ProQuad within 3 months before or at any time during pregnancy. Among these 5 reports, 4 cases were reported live births to healthy infants without birth defects and 1 case was lost to follow-up. Together with other varicella containing vaccines included in the VZV-Pregnancy Registry, no case of CVS following vaccination with varicella live attenuated virus vaccines have been reported and no pattern has been identified regarding timing of vaccination exposures or clustering by type of individual birth defects. However, it was noted by the CHMP that although no evidence of CVS as a consequence of vaccination has been reported, data were too limited to draw any conclusion.

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 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 (Wistar RA 27/3) against rubella varies between 0 and 1.6% (Bozzo et al. 2011[3]; Watson et al. 1998[4]).

[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

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]. 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 ProQuad 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.

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

Vaccination of immunocompromised individuals with live attenuated viral MMRV 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 ProQuad 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 selected immune deficiencies should receive MMRV vaccination.

The CHMP agreed that patients with various IgG subclass deficiencies are not able to develop an appropriate antibody response to vaccines including MMRV 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.

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[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

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

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 ProQuad, 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 :

"*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 concluded that the current contraindication for use of ProQuad 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.

Immunocompromised individuals

The section 4.3 should also reflect that vaccination with ProQuad 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

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

ProQuad is a quadrivalent vaccine which is indicated in vaccination of individuals from 12 months of age against measles, mumps, rubella and varicella viruses. Vaccination with ProQuad 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 ProQuad is 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 ProQuad 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.

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

The CHMP acknowledged that ProQuad 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 ProQuad 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 ProQuad 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 regard to the immunocompromised patients, the CHMP concluded that in view of the available data vaccination with ProQuad should continue to be contraindicated in severely impaired humoral and/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.

The CHMP recommended the amendment to the terms of the marketing authorisation for ProQuad 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 ProQuad 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, rubella and varicella vaccines.

The CHMP concluded

- that the data provided were too limited and poorly documented to draw any conclusion and therefore without any sufficient data ProQuad 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.
- that vaccination with ProQuad 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 ProQuad in accordance to the Product Information set out in annexes I, II, and IIIB.