Annex II

Scientific conclusions and grounds for variation to the terms of the Marketing Authorisations

Scientific conclusions

Overall summary of the scientific evaluation of the measles, mumps, rubella and varicella containing vaccines (see Annex I)

Background information

Monovalent and multivalent measles, mumps, rubella and/or varicella containing vaccines (MMRV) 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.

On the basis of the most recent published data on rubella containing vaccines, in particular for pregnant women Belgium national competent authorities considered it was 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.

Based on the above, Belgium national competent authorities triggered a referral under Article 31 of Directive 2001/83/EC on 9 March 2012, requesting the CHMP to review the benefit/risk of these vaccines in the above mentioned populations, i.e. pregnant women and subjects with immune deficiencies.

Scientific discussion

Pregnant women

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.

Data provided from post marketing surveillance and published literature did not show any safety concern with respect to spontaneous abortion or congenital malformations in pregnant women that were inadvertently vaccinated with MMRV vaccines and no case of CRS or CVS have been reported. However, it was noted by the CHMP that the data from post-marketing surveillance and pregnancy registry were limited due to the current contraindication in the product information and were too poorly documented to draw any conclusion.

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 case of CRS has been reported in more than 3500 susceptible women who were unknowingly in early stages of pregnancy when vaccinated against rubella. There is an estimated theoretical risk of severe malformations attributed to the rubella containing vaccine that varies between 0.5% and 1.3%.

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 intend to become pregnant should be advised to delay for 1 month following rubella vaccination[1]. Current data indicate that rubella IgM after vaccination peaks around 30 days after vaccination and IgG is also detectable.

[1]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

Having considered all available data, the CHMP is of the opinion that MMRV vaccination should continue to be contraindicated in pregnant women. Taking into account that rubella and varicella vaccination induce 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 CHMP also recommended the update of the product information 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 also be 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.

Immunocompromised subjects

Regarding the contraindication on immunocompromised subjects, an assessment of the safety of MMRV vaccines (based on experience to date) in subjects with various types of immune deficiencies (e.g. T-cell defects, sub-class deficiencies etc.) was provided by the Marketing Authorisation Holders (MAHs).

The CHMP considered that the contraindication should be harmonised and adjusted according to WHO guidance and scientific data and that although these vaccines are generally contraindicated in immunocompromised subjects, some individuals may benefit from vaccination.

The CHMP acknowledged that MMRV vaccines should remain contraindicated in patients with severely impaired humoral and/or cellular immune systems such as severe combined immunodeficiency (SCID) and agammaglobulinemia. However, the CHMP concluded 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.

Grounds for variation to the terms of the marketing authorisations

Whereas

- the CHMP considered the referral under Article 31 of Directive 2001/83/EC for monovalent and multivalent measles, mumps, rubella and varicella containing vaccines.
- 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 monovalent and multivalent MMRV vaccines 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 of the monovalent rubella vaccines and multivalent MMR vaccines.

- that vaccination with MMRV 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.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisations for which the relevant sections of the summaries of product characteristics and package leaflets are set out in Annex III for monovalent and multivalent measles, mumps, rubella and varicella containing vaccines (see Annex I).