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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zostavax

Zoster vaccine (live)

Procedure no: EMEA/H/C/000674/A-20/0052

Note

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

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Table of contents

1. Background information on the procedure

On the basis of the most recent published data on rubella containing vaccines, in particular when administered to 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 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, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 for Zostavax. The European Commission requested the CHMP on 15 March 2012 to assess the above concerns and its impact on the benefit/risk for Zostavax, to give its opinion on measures necessary to ensure the safe and effective use of Zostavax, and to conclude whether the marketing authorisation for this medicinal product should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

Zostavax is a live attenuated zoster vaccine. It is indicated for prevention of herpes zoster ("zoster" or shingles) and herpes zoster-related postherpetic neuralgia and for immunization of individuals 50 years of age or older. Zostavax has been authorised by the European Commission for prevention of herpes zoster and herpes zoster-related post-herpetic neuralgia since 19 May 2006.

On the basis of the most recent published data on rubella containing vaccines, in particular when inadvertently administered to pregnant women, it was considered justified to review whether all monovalent and multivalent measles, mumps, rubella and varicella (MMRV) vaccines which included Zostavax 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 Zostavax and therefore the current 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 varicella, 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. Zostavax vaccination in pregnancy

Vaccination with Zostavax is contraindicated in pregnant women. Therefore, only limited data are available on inadvertent exposure of pregnant women.

Data from the routine pharmacovigilance and enhanced surveillance through the Varicella-Zoster Virus (VZV)-Pregnancy Registry have indicated four reports of inadvertent exposure to Zostavax within 3 months before or at any time during pregnancy. Out of these, three were live births and one was lost to follow-up. Together with other varicella containing vaccines included in the VZV-Pregnancy Registry, no case of CVS following vaccination with live attenuated varicella virus vaccine 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.

As the prevalence of varicella antibodies increased with age, the foetal susceptibility to CVS is minimal following vaccination with Zostavax due to high VZV seroprevalence rates of women of 50 years and older.

The CHMP concluded that the available data 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 and not well documented to recommend any change to the current contraindication in pregnant women.

The CHMP therefore 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[1], 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. Zostavax vaccination in immunocompromised individuals

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

Based on evidence available from clinical trial with Zostavax and post marketing safety surveillance with a zoster live attenuated virus vaccine (Oka strain of VZV), the CHMP considered the contraindication of Zostavax in immunocompromised subjects justified.

Zostavax has been evaluated in one study in mild-to-moderate immunocompromised patients on chronic/systemic doses of corticosteroids where no specific concerns were reported following vaccination among any of the immunocompromised subjects. Another ongoing study is assessing Zostavax in HIV patients on potent combination antiretroviral therapy with conserved immune function.

[1] 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

From post-marketing safety surveillance, it was noted that the reported adverse events (AEs) of immunocompromised or possibly immunocompromised subjects were similar to those reported in immunocompetent individuals. In addition, no clinically important patterns or trends have been identified, and there have been no reports of disseminated VZV infections or reports of others AEs in which the presence of Oka vaccines-strain VZV has been identified via PCR through the VZV identification program.

The CHMP considered to keep the wording of the product information of Zostavax unchanged for immunocompromised subjects as it is indicated for immunization of individuals 50 years of age or older against zoster virus and used at higher dose than other varicella live attenuated vaccines.

Taking into account the overall available data, there is no sufficient evidence at this stage to amend the product information. The CHMP therefore concluded to maintain the contraindication and keep the special warnings unchanged.

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 varicella 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 also concluded that the contraindication should remain in this specific subpopulation.

In view of the above, the CHMP did not warrant a change in the product information for Zostavax regarding the vaccination in immunocompromised individuals.

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

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.

In addition, in section 4.4 (Special warnings and precautions for use) the wording on pregnancy should be deleted.

Package Leaflet

In line with the recommendation made in the SmPC, the section “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, any wording on pregnancy and breastfeeding should be deleted from the section “Warnings and precautions”.

3. Overall discussion and benefit/risk assessment

Zostavax is a live attenuated zoster vaccine which is indicated for prevention of herpes zoster (“zoster” or shingles) and herpes zoster-related postherpetic neuralgia and for immunization of individuals 50 years of age or older. Vaccination with Zostavax 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 published literature and available guidance, such as the WHO recommendation.

Regarding vaccination in pregnant women, it was noted that Zostavax is contraindicated in pregnant women and therefore only limited data of spontaneous abortion, malformations, varicella syndrome (CVS) following vaccination were available. Evidence of transplacental transmission of varicella wild-type virus is known. The evidence to date does not indicate a safety concern with respect to spontaneous abortion or congenital malformations related to the inadvertent administration of lives attenuated varicella vaccines in pregnant women. In addition, no cases of 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 varicella vaccines virus were lacking and too poorly documented to draw any conclusion.

The CHMP considers that an estimated theoretical risk of CVS 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 live attenuated varicella containing vaccines should be avoided in principle in pregnant women.

The CHMP concluded that the contraindication of Zostavax 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 Zostavax the CHMP considered that Zostavax should continue to be contraindicated and did not warrant a change in the product information for this special population.

4. Overall conclusion

Having considered the overall submitted data provided by the MAH, the CHMP concluded that Zostavax 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 instead of 3 months.

With regard to the immunocompromised patients, the CHMP concluded that in view of the available data vaccination with Zostavax should continue to be contraindicated in this population and did not warrant a change in the product information.

The CHMP recommended the amendment to the terms of the marketing authorisation for Zostavax 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 Zostavax initiated by the European Commission.

- the CHMP reviewed all available data regarding use in pregnant women and in immunocompromised patients of varicella containing vaccines, including the most recent publications and data from post-marketing surveillance for varicella live attenuated vaccines.

The CHMP concluded

- that the data provided were too limited and poorly documented to draw any conclusion and therefore Zostavax 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 the contraindication and the special warnings in the product information for immunocompromised individuals should remain unchanged.

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