Annex II

Scientific conclusions

Scientific conclusions

Varilrix is a lyophilised live virus vaccine containing as the active ingredient the attenuated Varicella Zoster Virus (VZV) Oka strain. Each dose contains not less than 103.3 pfu of vaccine virus at expiry.

Varilrix is authorised in twenty-one countries in the EU, as well as Iceland, Norway and United Kingdom (UK(NI)) (reference is made to Annex I) via purely national procedures.

Having analysed the available English translations of national PIs for this product, the MAH identified divergencies and has come to the conclusion that the above-mentioned medicinal product Varilrix (and associated names), does not have the same PIs across all EU Member States/ Iceland /Norway/UK(NI), where it has been authorised, with respect to indication, method of administration, contraindications, special warnings and precautions for use, interactions with other medicinal products, pregnancy and lactation, undesirable effects and pharmacodynamic properties.

In view of these divergences concerning the authorisation of the above-mentioned medicinal product, on 29 May 2020, the MAH for Varilrix and associated names, notified the European Medicines Agency (EMA) of a request for referral under Article 30 of Directive 2001/83/EC in order to harmonise these divergences across the EU.

Overall summary of the scientific evaluation by the CHMP

Only the most major changes are discussed in detail below. However, all sections of the PI have been harmonised.

Section 4.1 – Therapeutic Indications

Active immunisation against varicella in healthy individuals

To support the indication from 9 months of age, immunogenicity and safety data from study MMRV-018 where Varilrix was used in healthy children aged 9-10 months at first vaccination, were provided. In this study, subjects from 9 months of age received 2 doses (3 months apart) of either Priorix-Tetra, or Priorix co-administered with Varilrix. In brief, from this study it was concluded that 2 doses of Varilrix elicited an immune response in 100% of previously seronegative subjects; the safety results showed that Varilrix was well-tolerated in infants as of 9 months, and no safety concerns were identified.

The CHMP reviewed all available data and considered that children from 9 months of age can be vaccinated. However, vaccine efficacy against clinical disease has only been shown for children 12-22 months of age, but for not for younger children. For children 9-11 months only immunogenicity studies are available. Thus, it is considered more appropriate to indicate vaccination from 9 -11 months only in special circumstances.

Varilrix efficacy data, for the other age groups i.e. 12 months and above, are based on the large randomised multi-country study OKA-H-179 and its extension studies OKA-H-180 EXT179 Year 1, OKA-H-181 EXT179 Year 2 and OKA-H-182 EXT179 Years 4 to 10 conducted in healthy children aged 12-22 months at the time of the first vaccination who received 1 dose of Varilrix, 2 doses of Priorix-Tetra or 2 doses of Priorix as active control and were followed up until 10 years post-vaccination.

Effectiveness data for Varilrix are based on published data on effectiveness estimates against any, moderate and severe varicella disease after administration of 1 or 2 doses of varicella-containing vaccines in different real-world settings. The effectiveness of the varicella vaccine has been assessed in outbreak, case-control, database, observational and modelling studies, of which outbreak studies are the most numerous to estimate the effect of varicella vaccination in real-world settings.

CHMP having assessed all the data available concluded that the use of Varilrix in active immunisation against varicella in healthy individuals is justified and the indication is considered acceptable.

Post-exposure prophylaxis (PEP) indication

Varicella vaccination induces a fast immune response that makes post-exposure prophylaxis possible.

The main evidence supporting the efficacy in the above indication is derived from a study that examined the efficacy of postexposure vaccination with Varilrix [Mor, 2004[1]]. To support the PEP indication the MAH provided a summary of the data from this study.

This double-blind, placebo-controlled study showed that there was a significant, between-group difference, in the severity of disease among the children who developed varicella, with Varilrix providing an 80% protective effect against moderate/severe illness. However, the administration of Varilrix to children after their exposure to siblings with active varicella infection did not prevent the disease as 41% of children who received Varilrix within 72 h of exposure acquired varicella, a rate similar to that in the placebo group (45%).

The MAH also provided data from 2 more recent studies, where Varilrix and other Oka varicella strain vaccines are used, as additional evidence that Varilrix may prevent varicella or reduce the severity of the disease [Brotons, 2010[2], Pinochet, 2012[3]].

Additional evidence for PEP use of Varilrix comes from current recommendations from several Regulatory Authorities (e.g., WHO, EMA) and Public Health Agencies.

Based on the assessment of the data and the evidence provided, the CHMP concluded that the use of Varilrix in post-exposure prophylaxis is justified and the indication is considered acceptable.

Indication in patients at high risk of severe varicella

Clinical studies with the formulation stored at -20°C, and more recent studies with the reformulated Varilrix (stored at 2-8°C) indicate that Varilrix is immunogenic and well-tolerated in individuals with a range of chronic disorders or who are immunocompromised due to a disease or because they are on immunosuppressive treatment, although the seroconversion rate after vaccination might be reduced compared to healthy subjects in specific target populations. This observation highlighted that additional doses may be required in certain high-risk populations [Levin, 2008]. In all the groups studied, there was no evidence to suggest that vaccination with Varilrix adversely affected the course of the underlying disease.

Based on the assessment of the data and the evidence provided, the CHMP concluded that the use of Varilrix in individuals at high risk of severe varicella has been properly justified and the indication is considered acceptable.

However, CHMP concluded that the indication, regarding this population, in section 4.1 should read:

"In individuals at high risk of severe varicella (see sections 4.3, 4.4 and 5.1)",

as this is considered to be a better-defined indication.

[1] Mor M, Harel L, Kahan E, Amir J. Efficacy of postexposure immunization with live attenuated varicella vaccine in the household setting--a pilot study. Vaccine. 2004 Dec 2;23(3):325-8. doi: 10.1016/j.vaccine.2004.06.004. PMID: 15530676

[2] Brotons M, Campins M, Méndez L, Juste C, Rodrigo JA, Martínez X, Hermosilla E, Pinós L, Vaqué J. Effectiveness of varicella vaccines as postexposure prophylaxis. Pediatr Infect Dis J. 2010 Jan;29(1):10-3. doi: 10.1097/INF.0b013e3181b36022. PMID: 19841607.

[3] Pinochet C, Cerda J, Hirsch T, Mieres J, Inostroza C, Abarca K. Efectividad de la vacuna antivaricela como profilaxis post exposición en niños chilenos [Effectiveness of varicella vaccine as post exposure prophylaxis in Chilean children]. Rev Chilena Infectol. 2012 Dec;29(6):635-40. Spanish. doi: 10.4067/S0716-10182012000700008. PMID: 23412032.

The rest of the proposed text is considering to be explanatory and as such should be moved to other sections of the SmPC.

Section 4.2 – Posology and method of administration

Healthy individuals

Infants from 9 months to 11 months

Data supporting the posology for infants from 9 months to 11 months is based on study MMRV-018. As discussed in section 4.1 above, in this study subjects from 9 months of age received 2 doses of vaccine, 3 months apart.

CHMP assessed the data presented and concluded that the recommended posology in infants from 9 months to 11 months is adequate and has been appropriately justified.

Children from 12 months, adolescents and adults

The available immunogenicity data supporting the current 2-dose recommendation in children are based on studies OKA-H-186, MMRV-018, MMRV-046 and MMRV-047, in which a single dose of Varilrix was shown to be immunogenic when administered subcutaneously in healthy infants and children from 9 months of age up to 6 years of age, but the magnitude of the immune response was higher when 2 Varilrix doses were given.

Effectiveness of Varilrix in real-world settings was shown in several non-interventional studies with different study designs (epidemic onset, case-control studies, observational studies, databases, models) and confirmed a higher level of protection and a decrease in the occurrence of varicella cases following 2 doses of Varilrix compared to a single dose.

Based on the above data, CHMP concluded that a 2-dose schedule in infants and children from the age of 9 months as well as for adolescents and adults, in order to obtain optimal protection against varicella disease, has been appropriately justified.

Individuals at high-risk of severe varicella

The need for additional dose administration in individuals at high risk of severe varicella is based on clinical studies with Varilrix in subjects with a range of chronic disorders or who are immunocompromised due to a disease or immunosuppressive treatment. The data show that Varilrix is immunogenic in these populations, although the seroconversion rate after vaccination in specific target populations might be reduced compared to that in healthy subjects. Data from a GSK supported study in children with end-stage chronic liver disease indicate that the persistence of anti-varicella antibodies tended to relate to the clinical disease severity [Nithichaiyo, 2001[4]]. This observation highlights that additional doses may be required for certain individuals at high risk of severe varicella.

Regarding the number of additional doses to be potentially administered, these cannot be specified, since it is depending on the immunological response of each subject and should be defined on a case-by-case basis, while respecting the minimum interval of 4 weeks between subsequent doses. The number of doses should be defined up to the discretion of the treating physician. Periodic measurement of varicella antibodies after immunization may be helpful to identify those individuals who may benefit from re-immunization.

CHMP assessed the data presented and concluded that the posology recommendations for individuals at high-risk of severe varicella are adequate and have been appropriately justified.

[4] Nithichaiyo C, Chongsrisawat V, Hutagalung Y, Bock HL, Poovorawa Y. Immunogenicity and adverse effects of live attenuated varicella vaccine (Oka-strain) in children with chronic liver disease. Asian Pac J Allergy Immunol. 2001 Jun;19(2):101-5. PMID: 11699716.

Other Sections of the SmPC

The data supporting contraindications included in section 4.3 of the SmPC was discussed by the MAHs and the rational provided for keeping them in the SmPC was agreed by the CHMP for individuals with severe humoral or cellular (primary or acquired) immunodeficiency; for patients with a history of hypersensitivity to the active substance, to any of the excipients or to neomycin. Varilrix should also not be used during pregnancy and pregnancy should be avoided for 1 month after vaccination.

Section 4.4 of the SmPC (Warnings) has been summarized to include the below main categories: subjects suffering from acute severe febrile illness, occurance of syncope, anaphylatic reactions, use of alcohol and other disinfecting agents, post-exposure prophylaxis, protective immune response, breakthrough cases, transmission of the Oka varicella vaccine virus, rash in healthy contacts, individuals at high risk of severe varicella and disseminated varicella with internal organ involvement.

Interactions with other medicinal products (section 4.5 of the SmPC) have been summarised in interactions regarding tuberculin testing, interactions in individuals who have received immunoglobulins or a blood transfusion, interaction with salicylates and use with other vaccines.

The CHMP agreed on a common wording, on fertility, pregnancy and lactation (section 4.6 of the SmPC). No clinical data on fertility are available in humans.

A harmonised version of section 4.8 of the SmPC regarding adverse events has been agreed by the CHMP.

Sections 4.7 (effects on ability to drive and use machines), 4.9 (overdose), 5.1 (pharmacodynamic properties), 5.2 (pharmacokinetic properties) and 5.3 (preclinical safety data) were also harmonised.

The SmPC was also updated to be in line with the latest QRD template.

Package Leaflet

The Package Leaflet was amended in accordance with the changes made to the SmPC.

Grounds for the CHMP opinion

Whereas,

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the identified divergences for Varilrix and associated names, for the indications, posology and interactions, as well as the remaining sections of the product information.
- The committee reviewed the totality of the data submitted by the MAH in support of the proposed harmonisation of the product information.
- The committee agreed on a harmonised product information for Varilrix and associated names.

The CHMP recommended the variation to the terms of the marketing authorisations for which the product information is set out in Annex III for Varilrix and associated names (see Annex I).

The CHMP as a consequence, concluded that the benefit-risk balance of Varilrix and associated names remains favourable, subject to the agreed changes to the product information.