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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Product name: Varilrix and associated names

INN/active substance: live attenuated varicella virus (OKA strain)

Marketing authorisation holder: GlaxoSmithKline Biologicals (GSK Bio) group of companies and associated companies

Procedure number: EMEA/H/A-30/1499

Note:

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

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1. Background information

Due to the divergent national decisions taken by Member States concerning the authorisation of Varilrix and associated names, GlaxoSmithKline Biologicals (GSK Bio) notified the CHMP/European Medicines Agency on 29 May 2020 of a referral under Article 30 of Directive 2001/83/EC for Varilrix and associated names, in order to resolve divergences amongst the nationally authorised product information (PI) and thus harmonise it across the European Union (EU).

2. Scientific discussion

2.1. Introduction

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 $10^{3.3}$ 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) (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, 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.

2.2. Critical Evaluation

The MAH presented data from more than 40 clinical studies in subjects from the age of 9 months. Only the methods and results supportive for the data included in the proposed harmonised Varilrix PI were considered in the present procedure.

In most of the studies, Varilrix was the study vaccine. Data from several studies from the Priorix-Tetra clinical development program (in which Varilrix was co-administered with Priorix in the control group as well as studies for which data from GSK's MMRV vaccine are supportive for GSK's varicella vaccine) are also included to support efficacy, immunogenicity and safety data. It should be noted that Varilrix and Priorix-Tetra contain the same varicella virus strain. As such, it was considered to be appropriate to support efficacy, immunogenicity and safety of Varilrix with data obtained with Priorix-Tetra.

2.2.1. Product information

Section 4.1 – Therapeutic Indications

Varilrix was indicated for active immunisation against varicella, in healthy individuals, for post-exposure prophylaxis, in individuals at high risk of severe varicella and for vaccination of susceptible healthy close contacts of subjects at risk of severe varicella.

Active immunisation against varicella in healthy individuals

Regarding the indication for active immunisation against varicella in healthy individuals the main divergence identified concerned the age cut-off for administration, 9 months vs. 12 months of age. Also, some countries only allowed vaccination from 9 months under specific circumstances.

The MAH proposed a lower age limit of 9 months for Varilrix vaccination.

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.

Table 1 - Study MMRV-018: Anti-VZV antibody seroconversion rates and geometric mean titers (GMTs) by immunofluorescence assay (IFA) in initially seronegative subjects [according-to-protocol (ATP) cohort for immunogenicity]

Group	Timing	N	Seroconversion rates \geq 1:4				GMT		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
<i>Priorix-Tetra</i>	Pre	133	-	-	-	-	-	-	-
	PI(D42)	126	126	100	97.1	100	406.4	345.0	478.6
	PII(D126)	133	133	100	97.3	100	4074.7	3559.0	4665.1
<i>Priorix + Varilrix</i>	Pre	119	-	-	-	-	-	-	-
	PI(D42)	111	110	99.1	95.1	100	454.7	381.1	542.5
	PII(D126)	118	118	100	96.9	100	2289.8	1942.7	2698.9

The anti-VZV seroconversion rate was 100% after Dose 2 in both groups.

Anti-VZV antibody GMT ratios of post-Dose 2 over post-Dose 1 titres indicated that antibody responses in both groups increased after the administration of a second dose of varicella vaccine (see table 2). There was a significant increase in anti-VZV antibody GMTs following the second dose of vaccine (10.4-fold in the Priorix-Tetra group and 5.2-fold in the Priorix+Varilrix group).

Table 2 - Study MMRV-018: Anti-VZV antibody GMT ratios (post-dose 2 over post-dose 1) by IFA in initially seronegative subjects (ATP cohort for immunogenicity)

Group	N	Dose 1	Dose 2	Ratio Dose 2 over Dose 1		
		GMT	GMT	Value	95% CI	
					LL	UL
<i>Priorix-Tetra</i>	126	406.4	4210.2	10.36	8.65	12.41
<i>Priorix + Varilrix</i>	111	454.7	2364.3	5.20	4.14	6.53

The CHMP reviewed all available data and considered that children from age 9 months 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 (including national recommendations).

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, 2004¹]. 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. A prospective cohort study conducted in Spain in which 55 subjects received GSK's Varilrix and 12 subjects received Merck's Varivax has shown a vaccine effectiveness in preventing all forms of varicella, following immunisation within 5 days after contact of 62.3% (95%CI: 47.8-74.9) and effectiveness in preventing moderate and severe disease of 79.4% (95%CI: 66.4-88.9%) [Brotons, 2010²]. A controlled study conducted in Chile in which 33 children were followed-up after exposure to varicella of whom 15 received varicella vaccine (13 subjects received GSK's Varilrix and 2 subjects received Sanofi Pasteur's Biken) and 18 subjects were not vaccinated, has shown an overall effectiveness of varicella vaccine of 40% (95%CI: 1%-64%). The effectiveness for preventing moderate or severe disease was 63% (95%CI: 8%-85%) in the entire group and 77% (95%CI: 14%-94%) among children vaccinated during the first 3 days postexposure [Pinochet, 2012³].

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

The World Health Organisation (WHO) supports the use of varicella vaccines for PEP, as referred to in the immunogenicity, efficacy and effectiveness section of the WHO position paper on varicella and herpes zoster vaccines: "Post-exposure: Single-dose varicella vaccine administered within 3-5 days of exposure has proved to be highly effective for prevention of moderate or severe disease (79%-100%) but estimates varied for prevention of varicella disease of any severity (9%-93%)." Additionally, in

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 antivariela 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.

this document, WHO states the following in the WHO Position section: "Vaccination as soon as possible, within 3–5 days post-exposure, can be effective in preventing disease and should be considered in settings where routine varicella vaccination is implemented within the regular schedule." [WHO, 2014⁴].

In some EU countries, the use of varicella vaccines for PEP is part of the national vaccination recommendations. This the case, in Germany [STIKO, 2017⁵] and France [CSHPF, 2004⁶] where PEP use of varicella vaccines is common practice.

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

Varilrix was also indicated in patients at high risk of severe varicella in most EU countries. For the countries that did not have the indication in section 4.1 of the SmPC, vaccination of high-risk patients under certain circumstances, where the benefits outweigh the risks, was however mentioned in section 4.4 *Special warnings and precautions for use* of their national SmPCs.

The wording proposed by the MAH for the indication in patients at high risk of severe varicella in the Art. 30 harmonised SmPC was:

"Patients suffering from leukaemia, patients under immunosuppressive treatment (including corticosteroid therapy) for malignant solid tumour, for serious chronic diseases (such as chronic renal failure, auto-immune diseases, collagen diseases, severe bronchial asthma) or following organ transplantation, are predisposed to severe natural varicella. Vaccination with the Oka-strain has been shown to reduce the complications of varicella in these patients.

There is only limited data from clinical trials available for Varilrix (+4°C formulation) in patients at high risk of severe varicella; should vaccination be considered, it is advised that:

- maintenance chemotherapy should be withheld one week before and one week after immunisation of patients in the acute phase of leukaemia. Patients under radiotherapy should normally not be vaccinated during the treatment phase. Generally, patients are immunised when they are in complete haematological remission from the disease.*
- the total lymphocyte count should be at least 1,200 per mm³ or no other evidence of lack of cellular immune competence exists.*
- vaccination should be carried out a few weeks before the administration of the immunosuppressive treatment for patients undergoing organ transplantation (e.g. kidney transplant)".*

Varilrix (formulation stored at -20°C) received its first marketing authorisation in 1984 for use in immunocompromised subjects, and in some countries for healthy susceptible contacts or subjects considered at risk. The initial Varilrix indication was supported by clinical data from approximately 1000 healthy and immunocompromised subjects, summarised in a publication reporting data from 23 studies [André, 1984⁷]. This Varilrix formulation and indication was already approved in 8 EU countries prior to registration of the Varilrix formulation stored at + 4°C for the extension of the indication in healthy children, adolescents and adults, which was first approved on 17 October 1994 in Sweden. At the time of the registration of the new file for that extended indication, the results in the high-risk

⁴ Varicella and herpes zoster vaccines: WHO position paper, June 2014. Weekly epidemiological record. No. 25, 2014, 89, 265–288.

⁵ Ständige Impfkommission: Empfehlungen der Ständigen Impfkommission (STIKO) am Robert Koch-Institut. Epid Bull 2017;34:333 – 376 | DOI 10.17886/EpiBull-2017-065.1

⁶ Calendrier vaccinal 2004 Avis du Conseil supérieur d'hygiène publique de France, 19 mars 2004. N° 28-29/2004.

⁷ Andre FE. Summary of clinical studies with the Oka live varicella vaccine produced by SmithKline-RIT. *Biken J.* 27, 89 (1984)

population were briefly summarised, and additional EU countries approved the entire indication for use of Varilrix in healthy and immunocompromised subjects.

Meanwhile, the immunogenicity and safety of the refrigerator-stable Varilrix formulation has been assessed in multiple studies conducted in children and adults with stable immunosuppressive disorders or chronic disease, and their household contacts/stem-cell donors. Not all these studies were sponsored or supported by GSK, and therefore clinical study reports were not available for all studies, but all studies have been published and reviewed in several publications [Chiu, 2005⁸; Kreth, 2008⁹ and Levin, 2008¹⁰]. In brief, on the basis of these studies, it can be concluded that Varilrix was immunogenic in individuals with underlying diseases, including leukaemia, solid tumours, nephrotic syndrome, atopic dermatitis, chronic liver disease, end-stage renal disease, asthma treated by inhaled steroids and individuals post-transplantation, when administered during remission or when their disease is stable. However, compared to healthy individuals, seroconversion after a single dose was reduced in subjects with end-stage organ disease, malignancy, human immunodeficiency virus (HIV) infection, and in those who received inhaled steroid treatment.

In summary, 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.

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

CHMP concluded that the following paragraph should be moved to section 5.1, as it is considered to be a description of clinical efficacy: “*Patients suffering from leukaemia, patients under immunosuppressive treatment (including corticosteroid therapy) for malignant solid tumor, for serious chronic diseases (such as chronic renal failure, auto-immune diseases, collagen diseases, severe bronchial asthma) or following organ transplantation, are predisposed to severe natural varicella. Vaccination with the Oka-strain has been shown to reduce the complications of varicella in these patients*”.

⁸ Chiu SS, Lau YL. Review of the Varilrix varicella vaccine. *Expert Rev Vaccines*. 2005 Oct;4(5):629-43. doi: 10.1586/14760584.4.5.629. PMID: 16221065.

⁹ Kreth HW, Lee BW, Kosuwon P, Salazar J, Gloriani-Barzaga N, Bock HL, Meurice F. Sixteen years of global experience with the first refrigerator-stable varicella vaccine (Varilrix). *BioDrugs*. 2008;22(6):387-402. doi: 10.2165/0063030-200822060-00005. PMID: 18998756.

¹⁰ Levin MJ, Oxman MN, Zhang JH, Johnson GR, Stanley H, Hayward AR, Caulfield MJ, Irwin MR, Smith JG, Clair J, Chan IS, Williams H, Harbecke R, Marchese R, Straus SE, Gershon A, Weinberg A; Veterans Affairs Cooperative Studies Program Shingles Prevention Study Investigators. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. *J Infect Dis*. 2008 Mar 15;197(6):825-35. doi: 10.1086/528696. PMID: 18419349; PMCID: PMC4014857.

The rest of the text proposed by the MAH: *“There is only limited data from clinical trials available for Varilrix (+4°C formulation) in patients at high risk of severe varicella; should vaccination be considered, it is advised that:*

-maintenance chemotherapy should be withheld one week before and one week after immunisation of patients in the acute phase of leukaemia. Patients under radiotherapy should normally not be vaccinated during the treatment phase. Generally, patients are immunised when they are in complete haematological remission from the disease.

-the total lymphocyte count should be at least 1,200 per mm³ or no other evidence of lack of cellular immune competence exists.

-vaccination should be carried out a few weeks before the administration of the immunosuppressive treatment for patients undergoing organ transplantation (e.g. kidney transplant).”

should be moved to *Section 4.4 Special warnings and precautions for use*, as it concerns the description of precautions for use of Varilrix in this patient population.

Statement on the use of Varilrix according to official recommendations

Some PIs included a statement on the use of the vaccine according to local official recommendations.

In order to facilitate the use of the vaccine according to local official recommendations CHMP concluded that the sentence should be included in section 4.1 of the harmonized PI.

Healthy close contacts of subjects at risk of severe varicella

Additional wording was included in the PIs of most countries, to specify the recommendation of Varilrix for use in healthy close contacts of subjects at risk of severe varicella.

CHMP concluded that the statement should be deleted in its entirety since this is considered a Public Health recommendation rather than a properly defined indication.

The final agreed wording for the full section 4.1 of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.2 – Posology and method of administration

Posology

The MAH proposed, as part of the harmonisation, to keep the statement on the use of Varilrix according to official recommendations in section 4.2 of the SmPC.

The CHMP concluded that this statement should be included in section 4.2 as immunization schedules and epidemiological situations in each country may influence the use of the vaccine.

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

When the current Varilrix formulation (+4°C formulation) was first approved in 1994, a 1-dose schedule was recommended for children and a 2-dose schedule for adolescents (≥ 13 years of age) and adults. The 2-dose vaccination schedule in adolescents and adults was implemented to ensure optimal protection, as above 12 years of age it is known that the disease is more severe and the risk for complications related to varicella disease is higher [Gershon, 2013¹¹].

Later in the clinical development plan, the MAH revised the schedule to a 2-dose schedule also in infants and children, based on the available immunogenicity data with 2 doses of varicella vaccine in this age group.

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.

Although no efficacy data with 2 doses of Varilrix have been generated, the efficacy data of Priorix-Tetra obtained in the large randomised controlled study OKA-H-179 and its extension studies are considered supportive for the Varilrix 2-dose schedule. As Varilrix and Priorix-Tetra contain the same varicella virus strain, are formulated from the same varicella bulk and have the same end-of-shelf-life specification for varicella ($10^{3.3}$ PFU/dose). The comparison of data after 2 doses of varicella vaccine (Priorix-Tetra) with those after 1 dose of varicella vaccine (Varilrix) in this study indicates that 2 vaccine doses confer higher protection, especially against varicella disease of any severity. These data are also reflected in SmPC Section 5.1 of the harmonised PI.

In addition, effectiveness of Varilrix in real-world settings was shown in several noninterventional 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, 2001¹²]. 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

¹¹ Gershon AA, Gershon MD. Pathogenesis and current approaches to control of varicella-zoster virus infections. Clin Microbiol Rev. 2013 Oct;26(4):728-43. doi: 10.1128/CMR.00052-13. PMID: 24092852; PMCID: PMC3811230

¹² 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.

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.

Other paediatric population

The MAH proposed to include in section 4.2 the statement below to be in line with the current Quality Review of Documents (QRD) requirements in the EMA PI template (version 4.1, dated 02/2020):

“The safety and efficacy of Varilrix in infants less than 9 months of age have not yet been established. No data are available.”

The Spanish and Italian SmPCs contained a specific statement that Varilrix must not be administered to children under 9 or 12 months of age, respectively. The abovementioned statement according to the QRD template is considered to replace the statement in the Spanish SmPC, while the statement in the Italian SmPC is considered obsolete by providing supportive data in the 9-10 months old age group (study MMRV- 018, please see above).

In addition, the Spanish SmPC stated that: “There is not sufficient data to determine the long-term protective efficacy of the vaccine. However, currently, there is no evidence that additional doses are systematically required after completing a prescription of two doses.” However, since long-term efficacy data from study OKA-H-182 up to Year 10 has been provided (please see section 5.1 below), this statement is not applicable anymore.

Interchangeability

The interchangeability of varicella vaccines to complete the 2-dose vaccination course has been studied in children in studies MMRV-046 and MMRV-047.

Study MMRV-046 showed good immunogenicity in children who received a second dose of Varilrix following initial vaccination with Priorix-Tetra. After the first dose of Priorix-Tetra in study MMRV-046, the anti-VZV seroconversion rate in initially seronegative subjects was 97.8% with a post-vaccination GMT of 90.5. After administration of Varilrix 6 weeks later, all subjects had seroconverted and the GMT increased 13-fold compared to post-Dose 1 (see table 3 below).

Table 3 - Studies OKA-H-186, MMRV-018, MMRV-046 and MMRV-047: Seroconversion/Seroresponse rates and GMT/ geometric mean concentration (GMC) in initially seronegative subjects* aged 9 months to 6 years after vaccination with a first and a second dose of Varilrix in children [IFA and enzyme-linked immunosorbent assay (ELISA), ATP immunogenicity cohort]

Study Number	Dose Vaccine	Time point	N	Seroconversion/Seroresponse			GMT/GMC			GMT Fold increase	
				n	%	95% CI		value	95% CI		
						LL	UL		LL		UL
Anti-varicella IgG immune response (ELISA) after 2 doses of Varilrix											
OKA-H-186	Varilrix with HSA	D42	115	103	89.6	82.5	94.5	110.7	98.4	124.6	-
		D84	114	114	100	96.8	100	999.2	877.3	1138.1	9.0
Anti-varicella IgG immune response (IFA ≥50 mIU/mL) after 2 doses of Varilrix or Varilrix as second dose											
OKA-H-186	Varilrix with HSA	D42	115	114	99.1	95.3	100	154.3	128.7	185.0	-
		D84	112	112	100	96.8	100	1395.4	1183.0	1645.9	9.0
MMRV-018	Priorix + Varilrix	D42	111*	110	99.1	95.1	100	454.7	381.1	542.5	-
		D126	118*	118	100	96.9	100	2289.8	1942.7	2698.9	5.0
MMRV-046	Group 1: Priorix + Varilrix	D42	177*	174	98.3	95.1	99.6	112.5	95.3	132.7	-
	Group 1: Varilrix	D84	177*	177	100	97.9	100	1275.1	1100.7	1477.2	11.3
	Group 2: Priorix-Tetra	D42	178*	174	97.8	94.3	99.4	90.5	74.0	110.8	-
	Group 2: Varilrix	D84	176*	176	100	97.9	100	1198.7	1023.1	1404.4	13.2
MMRV-047	Priorix + Varilrix (2 nd dose) in MMR +V primed subjects	Pre	188	187	99.5	97.1	100	97.4	78.9	120.4	-
		D42	188	188	100	98.1	100	2555.1	2187.0	2985.0	26.2

Study MMRV-047 showed good immunogenicity in children who received a second dose of Varilrix after initial vaccination with any varicella vaccine (Varilrix or Varivax or a varicella vaccine from unknown manufacturer). In this study, anti-VZV GMTs markedly increased (26-fold) after the second dose

irrespective of the varicella vaccine given prior to study start (see table 3). A strong boosting effect was observed after a dose of varicella-containing vaccine in children previously primed with an MMR and varicella vaccine.

Based on data from studies MMRV-046 and MMRV-047, it can be concluded that Varilrix may be used to complete a primary immunisation course started with another varicella containing vaccine, either monovalent or combined as MMRV, or alternatively, that Varilrix may be followed by a dose of another varicella containing vaccine.

CHMP concluded that the study results demonstrated interchangeability and considered the statement in section 4.2 adequate.

Method of administration

The MAH proposed to align the statement on the method of administration with the German SmPC, which is the only country who had so far approved the intramuscular (IM) route of administration (evaluated within extension variation DE/H/0468/001-002/X/092 as aligned with the approved wording in the Priorix-Tetra EU MRP SmPC) in addition to the subcutaneous route that was already approved in all other countries.

The MAH proposed to include the IM route of administration in the Art 30 harmonised SmPC to avoid off-label use of Varilrix. Live attenuated vaccines such as the varicella vaccine are usually given SC, whereas most paediatric vaccines are inactivated vaccines and typically given IM. As SC administration is less commonly performed and can be perceived as challenging compared to IM administration, it is likely that live-attenuated vaccines might be inadvertently given intramuscularly. As it is commonly acknowledged that the response to live attenuated vaccines administered by the SC route will not be affected if the vaccines are administered by the IM route [Kroger, 2011¹³], the MAH proposed to add the IM route of administration to the currently recommended SC administration route to allow flexibility with respect to administration route for Varilrix.

The immunogenicity of Priorix-Tetra (containing the same varicella strain as Varilrix) administered via IM versus SC route was evaluated in study MMRV-048 in 283 healthy children aged 11-21 months (based on the ATP cohort for immunogenicity).

The primary objective of this study was met as the IM administration of Priorix-Tetra was demonstrated to be non-inferior to the SC administration in terms of seroconversion rate for anti-VZV antibodies after the second vaccine dose in initially seronegative subjects. Moreover, the anti-VZV antibody GMTs were comparable between the 2 study groups (3388.8 [95% CI: 2768.3, 4148.4] in the IM group and 2575.7 [95% CI: 2081.5, 3187.4] in the SC group). All initially seronegative subjects in both groups were seropositive for anti-varicella antibodies following Dose 2, representing a seroconversion rate of 100% (95% CI: 97.2, 100) in both groups.

Additionally, as it is known that individuals with a bleeding disorder are at high risk of developing hematomas at IM injection sites [Kroger, 2011], IM administration should be avoided in persons with bleeding disorders in whom the SC route should be used. Therefore, in line with current recommendations [CDC, 2011¹⁴], a recommendation for SC administration in patients with bleeding disorders has been added to the wording for the method of administration in section 4.2.

¹³ Kroger AT, Sumaya CV, Pickering LK, Atkinson WL. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2011; 60: 1-64.

¹⁴ Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(No. 2)

The CHMP concluded that the data provided is adequate to justify the IM use of Varilrix and the statement on IM administration should be included in section 4.2.

The final agreed wording for the full section 4.2 of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.3 – Contraindications

All contraindications (CI) included in the harmonised SmPC have been reviewed and are discussed below.

- i. Varilrix is contraindicated in individuals with severe humoral or cellular (primary or acquired) immunodeficiency such as (see also section 4.4):*
 - *subjects with immunodeficiency states with a total lymphocyte count less than 1,200 per mm³;*
 - *subjects presenting other evidence of lack of cellular immune competence (e.g. patients with leukaemias, lymphomas, blood dyscrasias, clinically manifest HIV infection);*
 - *subjects receiving immunosuppressive therapy including high dose of corticosteroids;*
 - *severe combined immunodeficiency;*
 - *agammaglobulinemia;*
 - *AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage in children below 12 months: CD4+ <25%; children between 12-35 months: CD4+ < 20%; children between 36-59 months: CD4+ < 15%.*

The contraindication in individuals with severe humoral or cellular immunodeficiency is in line with the CHMP recommendations made during the Article 31 referral assessment for varicella-containing vaccines (procedure number: EMEA/H/A-31/1333, approved on 27 June 2013).

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 and mandated the following wording:

“Severe humoral or cellular (primary or acquired) immunodeficiency, e.g. severe combined immunodeficiency, agammaglobulinemia and AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage in children below 12 months: CD4+ <25%; children between 12-35 months: CD4+ < 20%; children between 36-59 months: CD4+ < 15% (see section 4.4).”

Therefore, this wording has been included as such in the proposed harmonised Varilrix PI.

- ii. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to neomycin. However, a history of contact dermatitis to neomycin, is not a contraindication.*

In line with the SmPC guideline a CI on hypersensitivity to the active substance or to any of the excipients or residues from the manufacturing process should be mentioned. As such, CHMP concluded that this CI should be kept as part of the harmonised PI.

In addition, a clarification that a history of contact dermatitis to neomycin is not a contraindication has been added. Since Varilrix might contain traces of neomycin sulphate, hypersensitivity to neomycin is listed as a contraindication in the proposed PI. However, allergy to neomycin is commonly manifested as contact dermatitis, which is considered as less severe.

Therefore, the harmonised PI states that a history of contact dermatitis to neomycin is not a contraindication. This statement was already included in most countries, with the exception of the PI in Austria that did not specify neomycin, and as a consequence did not include that contact dermatitis to neomycin is not a contraindication.

- iii. *Varilrix is contraindicated in subjects having shown signs of hypersensitivity after previous administration of varicella vaccine.*

Cases of hypersensitivity and cases of anaphylactic reaction have been reported following Varilrix vaccination. Therefore, as a precautionary measure and since subjects with history of hypersensitivity are at risk, a contraindication to subjects with history of hypersensitivity following previous vaccination with varicella vaccine should be included.

Based on the justification presented by the MAH the CHMP concluded that this CI should be retained.

- iv. *Pregnancy. Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).*

There are no clinical data on the use of Varilrix during pregnancy or lactation. The data on exposure to Varilrix prior or during pregnancy from spontaneous reports during post-marketing submissions have not indicated a safety concern with respect to spontaneous abortion, miscarriage, stillbirth, immaturity, low birth weight or congenital malformations related to the inadvertent administration of Varilrix to pregnant women. However, as live viral vaccines may pose a theoretical risk to the foetus, Varilrix vaccination remains contraindicated in pregnant women.

The CHMP also reviewed several divergences from the local SmPCs. These divergences are discussed and presented below.

Acute, febrile illness

Several countries have a statement that administration of Varilrix should be postponed in subjects suffering from acute severe febrile illness in the contraindication section. The MAH considers that this statement is a precaution and proposed to have this statement in the SmPC Section 4.4 Special warnings and precautions for use as part of the Art. 30 harmonised SmPC (and remove it from SmPC Section 4.3 Contraindications).

As the statement refers that vaccination should be postponed (and not contraindicated) CHMP concluded that the statement should be included in section 4.4 of the SmPC and not section 4.3 (please see discussion below in section 4.4)

Additional country-specific contraindications not included the harmonised SmPC

- Fructose intolerance
- Breastfeeding (from the Spanish SmPC)
- Family history of congenital or hereditary immunodeficiency, unless it can be demonstrated that the immune system is functioning (from the Danish SmPC)

As no safety signal after vaccination with Varilrix in subjects with these specific conditions has been identified so far (refer to Varilrix PSUR with procedure number: PSUSA/00010473/201903, approved on 28 November 2019), the MAH proposed to not include these CIs in the harmonised SmPC.

CHMP concluded that since there is no evidence that would justify the retain these CIs and no specific safety risks could be identified, these can be removed.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.4 – Special warnings and precautions for use

Several warnings were in place in some or all MSs with slightly different wording. These have been reviewed and harmonised accordingly.

Traceability

This statement is included according to the current QRD requirements.

Acute febrile illness

For the statement on acute febrile illness, the MAH proposed to amend the sentence on minor infection in the harmonised SmPC, to align it with the wording used in the Priorix and Priorix-Tetra SmPC as the MAH considered it more appropriate.

The most commonly used wording among the EU SmPCs was:

"In healthy subjects the presence of a minor infection, however, is not a contra-indication for vaccination."

The proposed harmonised text is:

"However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination."

The CHMP considered this change as acceptable as the new wording is a clarification of the wording already existing in most SmPCs.

Syncope

All national PIs already included a warning for syncope with some small divergences on the exact wording used.

The wording included in the harmonised PI is aligned with the CHMP recommendation made following review of 3rd Periodic Safety Update Report (PSUR) for Cervarix (GSK's HPV-16/18 L1 VLP AS04 vaccine).

As syncope has been reported with almost all vaccines in the GSK portfolio that are administered via injection and injuries have been associated with this event, a worksharing procedure EMEA/H/C/xxxx/WS/0153 was submitted for all injectable GSK vaccines and approved by CHMP on 26 October 2012. The wording in SmPC Section 4.4 of the harmonised PI has been aligned accordingly.

Anaphylactic reaction

The MAH proposed to include the following statement:

"As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine".

Some countries have wording similar to the proposed harmonised SmPC in Section 4.4 Special warnings and precautions for use of their local SmPC. Additional wording on an observation period of 30 minutes after vaccination is included in some countries as well, whereas an observation period of 20 minutes is included in the national SmPC of Iceland and Norway. Reference is also made to an additional subsection in Section 4.8 of some national SmPCs for "Treatment in case of anaphylactic reaction", while the treatment to provide is specified in this section in the SmPC of IS, IT and NO. This additional information is not proposed to be included in the harmonised SmPC as the treatment details are left at the discretion of the prescriber.

Since this statement is applicable to any injectable vaccine, the inclusion of this statement in the harmonised SmPC is considered acceptable by CHMP.

Alcohol and other disinfecting agents

Regarding the statement, *"Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they can inactivate the attenuated viruses in the vaccine"*, CHMP agreed that it should be present in the harmonised SmPC as this statement is applicable to any live attenuated viral vaccine.

Post-exposure prophylaxis

As discussed in section 4.1, regarding the PEP indication, the clinical data did not show complete protection after PEP use of Varilrix, as such the statement on the limited protection from PEP with Varilrix within 72 hours should be kept in the harmonised SmPC Section 4.4 Special warnings and precautions for use:

"Limited protection against varicella may be obtained by vaccination up to 72 hours after exposure to natural disease (see section 5.1)."

In addition, a reference to section 5.1 Pharmacodynamic properties where the relevant supporting data are provided has been added.

Protective immune response

CHMP agreed that a statement warning that a protective immune response may not be elicited in all vaccines should be included in the harmonised SmPC as this statement is applicable to all vaccines.

Breakthrough cases

Data on the characteristics of confirmed varicella cases in vaccinated and control group from study OKA-H-182 EXT179 Years 4 to 10 were presented.

The observed severity of breakthrough cases in both the 2-dose and 1-dose groups was lower as compared with the severity of the cases occurring in the control group: the mean severity scale scores (according to the modified Vasquez scale) were 4.86 in the Priorix-Tetra group and 5.36 in the Varilrix group, compared with 7.67 in the Priorix control group for confirmed varicella cases.

Among the children who developed a breakthrough case of varicella in the Priorix-Tetra and Varilrix groups, the majority (88.2% and 75.9%, respectively) had ≤ 50 lesions compared with 35.8% of subjects in the Priorix control group, in which 31.8% of subjects had 51-100 lesions, 28.4% of subjects had 101-500 lesions and 3.7% of subjects had > 500 lesions. Also, concurrent fever was less frequently reported by subjects with a breakthrough varicella case in the Priorix-Tetra and Varilrix groups (2.6% and 8.5% of subjects with temperature 38.8-39.9°C, respectively, and 2.6% and 0.9%

of subjects with temperature $\geq 40.0^{\circ}\text{C}$, respectively) compared with subjects in the *Priorix* control group (26.4% of subjects with temperature $38.8\text{-}39.9^{\circ}\text{C}$ and 2.8% of subjects with temperature $\geq 40.0^{\circ}\text{C}$).

Based on this data the MAH proposed to include the following statement in the harmonised SmPC (which is in line with most national SmPCs): "*As for other varicella vaccines, cases of varicella disease have been shown to occur in persons who have previously received Varilrix. These breakthrough cases are usually mild, with a fewer number of lesions and less fever as compared to cases in unvaccinated individuals*", which was endorsed by CHMP.

Transmission

The limited data available indicate that transmission of the Oka varicella virus from varicella vaccinees is extremely rare, as reflected by the statement in SmPC Section 4.4 of the harmonised PI. Among the hundreds of millions of doses of administered Oka varicella vaccines, only a few cases of transmission of Oka virus from healthy vaccinees to contacts were documented so far [Gershon, 2013].

The wording to specify that "Transmission of the Oka varicella vaccine virus from a vaccinee who does not develop a rash to seronegative contacts cannot be excluded" was included based on the review of the reported cases of varicella virus transmission from vaccinees without rash to healthy contacts [Kluthe, 2012¹⁵]. Since the impact on risk-benefit is thought to be limited in view of the low frequency of this event, the MAH re-classified this a non-important risk, as agreed with the Pharmacovigilance Risk Assessment Committee (PRAC) in the PSUR AR for varicella vaccine (live) (procedure number: PSUSA/00010473/201903, approved on 28 November 2019).

For the proposed PI, the Company selected the wording on transmission

The wording in the harmonised PI is in line with the approved *Varilrix* SmPC in Germany as it is considered that this wording is the most complete and relevant information for the prescriber amongst all individual national SmPCs.

Rash in healthy contacts

In the rare cases where healthy contacts of vaccinees report symptoms, they only present with a mild form of varicella disease. Moreover, based on the well-established safety experience with *Varilrix*, there is no evidence that the virus would become more virulent in healthy contacts of vaccinated subjects. As such, the following statement has been added to the harmonised SmPC:

"The mild nature of the rash in the healthy contacts indicates that the virus remains attenuated after passage through human hosts."

CHMP endorsed the MAH's proposal as it considers relevant to provide this information to the prescriber.

Individuals at high-risk of severe varicella

The statement on individuals at high risk of severe varicella in SmPC Section 4.4 of the harmonised PI is based on data in immunocompromised (IC) individuals, in whom varicella virus infection could cause severe disseminated life-threatening infection. Clinical studies with *Varilrix* (both frozen and $+4^{\circ}\text{C}$ formulations) indicate that this vaccine is immunogenic and well-tolerated in individuals with a range of chronic and immunosuppressive disorders when vaccinated during remission or under stable conditions after or during treatment [André, 1984; Kreth, 2008]. Although the seroconversion rate after vaccination might be reduced compared to healthy subjects in specific target populations, data have

¹⁵ Kluthe M, Herrera A, Blanca H, Leung J, Bialek SR, Schmid DS. Neonatal vaccine-strain varicella-zoster virus infection 22 days after maternal postpartum vaccination. *Pediatr Infect Dis J.* 2012 Sep;31(9):977-9. doi: 10.1097/INF.0b013e31825d2a1b. PMID: 22572750.

shown that for IC populations who are predisposed to severe varicella, complications of varicella may be reduced through vaccination [Gershon, 2013].

Although Varilrix is contraindicated in subjects with severe humoral or cellular (primary or acquired) immunodeficiency, these limited data show that for some IC populations the benefits of vaccination with Varilrix may outweigh the risks. For these reasons, SmPC Section 4.4 of the proposed PI includes wording to inform physicians that IC patients should be monitored carefully when, upon a careful, case-by-case analysis of the risks and benefits, the decision of vaccinating is taken.

The harmonised wording is in line with the CHMP recommendations made during the Article 31 referral assessment for varicella-containing vaccines (procedure number: EMEA/H/A-31/1333, approved on 27 June 2013), i.e., the CHMP requested that a warning should be added for MMRV vaccines 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.

Disseminated varicella with internal organ involvement

It has been observed on rare occasions that the live attenuated varicella vaccine can disseminate into the body and cause severe complications, mainly in IC individuals, as reflected by the statement in SmPC Section 4.4 of the harmonised PI. In IC individuals, the live varicella vaccine, although attenuated, could cause an infection similar to natural varicella and its complications. Disseminated varicella disease has been reported in 6 IC children who were immunised with an Oka-based varicella vaccine (Varivax) before an immune defect was diagnosed [Galea, 2008¹⁶]. In addition, severe vaccine-related varicella occurred in some IC children who received varicella vaccine while receiving chemotherapy for solid tumours [Takahashi, 1986¹⁷].

Bhalla et al described the first case of disseminated infection due to the Oka strain of varicella vaccine in an adult with history of non-Hodgkin lymphoma who had received an autologous peripheral blood stem cell transplant in 2006, with relapse of disease in 2009 [Bhalla, 2011¹⁸]. Banovic et al described disseminated varicella infection caused by varicella vaccine strain in a child with low invariant natural killer T cells and diminished CD1d expression [Banovic, 2011¹⁹].

Based on the available data, "*Disseminated varicella with internal organ involvement following vaccination with Oka varicella vaccine strain mainly in immunocompromised subjects*" was identified as an important potential risk, as agreed with PRAC in the PSUR AR for varicella vaccine (live) (procedure number: PSUSA/00010473/201903, approved on 28 November 2019).

Therefore, CHMP concluded that this statement should be reflected in SmPC Section 4.4 of the harmonised PI.

Method of administration

In several countries, the statement that Varilrix must not be administered intravascularly or intradermally is repeated in the method of administration section of the SmPC, whereas in other

¹⁶ Susan A. Galea, Ann Sweet, Paul Beninger, Sharon P. Steinberg, Philip S. LaRussa, Anne A. Gershon, Robert G. Sharrar, The Safety Profile of Varicella Vaccine: A 10-Year Review, *The Journal of Infectious Diseases*, Volume 197, Issue Supplement_2, March 2008, Pages S165–S169, <https://doi.org/10.1086/522125>

¹⁷ Takahashi M. Clinical overview of varicella vaccine: development and early studies. *Pediatrics*. 1986 Oct;78(4 Pt 2):736-41. PMID: 3020493.

¹⁸ Preeti Bhalla, A. Gershon, J. Chen, P. LaRussa, S. Steinberg, G. Forrest. Disseminated Varicella infection due to Oka -vaccine (vOka) strain of varicella-zoster virus (VZV) in an adult. Poster Abstract Session: Challenges in Vaccinology and Vaccine Exploration; October 21, 2011

¹⁹ Banovic T, Yanilla M, Simmons R, Robertson I, Schroder WA, Raffelt NC, Wilson YA, Hill GR, Hogan P, Nourse CB. Disseminated varicella infection caused by varicella vaccine strain in a child with low invariant natural killer T cells and diminished CD1d expression. *J Infect Dis*. 2011 Dec 15;204(12):1893-901. doi: 10.1093/infdis/jir660. Epub 2011 Oct 31. PMID: 22043019.

SmPCs, this statement is only stated in that section. All other countries have similar wording with minor differences.

Different routes of administration may have a different safety profile. The MAH considers it appropriate to highlight that these two routes of administration must not be used for Varilrix, as their efficacy and safety has not been tested in clinical trials. The CHMP agreed with this approach and the statement should be included in section 4.4 of the harmonised SmPC.

Fructose intolerance

Several SmPCs included a warning in case of fructose intolerance, and the Finish SmPC included the following wording in the context of sorbitol as excipient: *"This vaccine contains 6 mg sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account."*

Based on the EMA guidance in the "Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use" issued on 9 October 2017 (EMA/CHMP/460886/2014), and taking into account the outcome of previous regulatory actions for similar medicinal products (such as Priorix and Priorix-Tetra), the MAH proposed to not include this statement in the harmonised SmPC, as Varilrix contains only a low amount of sorbitol (6 mg), and is not for intravenous or daily use.

This was endorsed by CHMP and as such the warning on fructose intolerance has been removed.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.5 – Interaction with other medicinal products and other forms of interaction

Tuberculin testing

It is known that concurrent viral infections in general (including varicella) can cause false negative results on tuberculin test by temporary reduction of the tuberculin sensitivity of the skin. As this reduced reaction may persist for up to 6 weeks, tuberculin tests should not be performed within this period after immunisation so as to avoid false negative results. Therefore, it should be performed either prior to or at the same time as immunization or postponed for 6 weeks. Although there is no information on the effect of varicella vaccine on reactivity to a tuberculin skin test, measles vaccination can reduce sensitivity because of mild suppression of the immune system. Therefore CHMP concluded that, as a conservative approach this statement should be part of the harmonised SmPC (of note, most countries already had this wording).

Immunoglobulins or blood transfusion

Human immunoglobulin may inhibit the immune response to live viral vaccines. In addition, low levels of anti-VZV antibodies may be present in the blood product, which could impair the immune response to the live viral vaccine.

As such, CHMP concluded that a statement that, in individuals who have received immunoglobulins or a blood transfusion, vaccination should be delayed for at least three months because of the likelihood of vaccine failure due to passively acquired varicella antibodies, should be included in the harmonised SmPC.

Salicylates

The statement that salicylates are to be avoided for 6 weeks after varicella vaccination as Reye's syndrome has been reported following the use of salicylates during natural varicella infection is supported by literature data. It has been observed that Reye's syndrome is usually preceded by a viral

illness, particularly varicella or influenza B, and has been associated with the use of aspirin during such infections [Larsen, 1997²⁰]. The number of cases declined in countries where there has been a public education campaign and aspirin products have been withdrawn from sale.

Although the cause of Reye's syndrome is unknown, it is shown to be associated with the use of salicylates administered to recover from fever-causing viral infections, such as influenza or chickenpox, especially in children. Therefore, CHMP concluded that this statement should be maintained in the harmonised SmPC.

Use with other vaccines

Healthy individuals

Most of the national SmPCs, contained a broad wording that Varilrix can be administered at the same time as any other vaccine, with some countries specifying some of these vaccines.

It was considered to be valuable information to the Health Care Professionals (HCPs) and patients to be informed on the precise list of vaccines that can be given concomitantly instead of the broad wording that Varilrix can be given with any other vaccine. Hence, the MAH provided the available co-administration studies to update this section of the harmonised SmPC, in order to clarify exactly which vaccines can be administered with Varilrix, based on scientific evidence.

The harmonised SmPC should list the vaccines for which there are clinical study data for coadministration as it was also considered that this broad wording is too categorical. It could also lead to the administration of Varilrix with a newly authorised live vaccine in the future without coadministration information and that could lead to unknown adverse events or interference.

Of note, co-administration with varicella-containing vaccines is included in the PI of many other vaccines (including GSK's Priorix-Tetra).

As such, the MAH provided immunogenicity and safety data from clinical studies where varicella-containing vaccines were co-administered with other vaccines to support the update of Section 4.5 of the Varilrix SmPC during the harmonisation procedure.

After having reviewed the submitted data and the MAH's response the CHMP concluded that the evidence submitted supported the inclusion of the following vaccines in the SmPC: measles-mumps-rubella vaccine (MMR), diphtheria-tetanus-acellular pertussis vaccine (DTPa), reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa), *Haemophilus influenzae* type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), hexavalent vaccine (DTPa-HBV-IPV/Hib), hepatitis A vaccine (HAV), meningococcal serogroup B vaccine (Bexsero), meningococcal serogroup C conjugate vaccine (MenC), meningococcal serogroups A, C, W and Y conjugate vaccine (MenACWY) and pneumococcal conjugate vaccine (PCV).

If a measles vaccine is not given at the same time as Varilrix, there should be an interval of at least one month between the administration of these vaccines as the measles vaccine may lead to short-term suppression of the cellular immune response. This precaution is included because of the known immunosuppressive effect of wild-type measles infection in terms of cellular immune response, it might be assumed that short-term suppression of the cellular immune response by vaccination with an attenuated measles virus might occur. However, measles vaccination is not reported to be associated with clinically significant immunosuppression [Griffin, 2010²¹].

²⁰ Larsen SU. Reye's Syndrome. *Medicine, Science and the Law*. 1997;37(3):235-241. doi:[10.1177/002580249703700308](https://doi.org/10.1177/002580249703700308)

²¹ Griffin DE. Measles virus-induced suppression of immune responses. *Immunol Rev*. 2010 Jul;236:176-89. doi: 10.1111/j.1600-065X.2010.00925.x. PMID: 20636817; PMCID: PMC2908915.

Individuals at high-risk of severe varicella

No data are available to support safety and immunogenicity of concomitant administration of multiple live attenuated vaccines in high-risk patients.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.6 – Fertility, pregnancy and lactation

Pregnancy

The 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 who were inadvertently vaccinated with monovalent or combined MMRV vaccines. However, it was noted that the data from post-marketing surveillance and pregnancy registry were limited due to the current contraindication in the PI and were too poorly documented to draw any conclusion.

Breast-feeding

There are no data regarding use in breast-feeding women.

Although no data on transmission of Varilrix from the mother to the child by breastfeeding are available so far, it is considered a theoretical risk for varicella vaccines. As such, CHMP concluded that a statement should be included in the harmonised SmPC (in line with the wording already included in some national SmPCs).

Fertility

No data available

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.7 – Effects on ability to drive and use machines

No studies on the effects of Varilrix on the ability to drive and use machines have been performed.

However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

As such, CHMP concluded that this should be reflected in the harmonised PI.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.8 – Undesirable effects

Clinical trial data

Healthy individuals

In the national SmPCs, safety data from clinical studies were supported by a pooled safety analysis provided as variation procedures, meanwhile approved in all countries. Hence, no major discrepancies with the proposed harmonised SmPC wording were found regarding the information included in the national SmPCs.

The overall safety evaluation of Varilrix after SC administration in healthy subjects is based on a review of pooled data from 29 studies conducted in infants and children from 9 months to 12 years of age (1-dose schedule as per previous posology in children) and adolescents and adults from 13 years to 79 years of age (mostly 2-dose schedule). These studies evaluated safety data from 4633 subjects who received Varilrix, representing a total of 5369 doses.

These data were used to develop the safety information from clinical trials as provided in SmPC Section 4.8 "Undesirable effects" of the proposed harmonised Varilrix PI. Importantly, only study groups which received Varilrix alone, without the concomitant administration of other vaccines, were considered for the analysis of adverse events (AEs) based on this pooling. In parallel with this large pooling, AEs reported through post-marketing surveillance (PMS) and deemed possibly related to the administration of Varilrix were added to the core safety information from post-marketing data in SmPC Section 4.8 "Undesirable effects" of the proposed harmonised PI.

In addition, a statement on the safety profile of the IM presentation was added to the harmonised SmPC. To provide the evidence on the reactogenicity and safety of *Varilrix* after IM administration, results from study MMRV-048 evaluating the safety of *Priorix-Tetra* (containing the same varicella strain) when administered via IM versus SC route in healthy children aged 11-21 months were presented.

Individuals at high risk of severe varicella

In addition, data on the reactogenicity and safety of Varilrix after SC administration to individuals with underlying medical conditions at high risk of severe varicella are presented based on 1 GSK-sponsored study (OKA-H-178) and 3 GSK-supported clinical studies as well as published data from clinical studies not supported or partially supported by GSK.

The CHMP reviewed all the data submitted by the MAH in order to support the list of adverse reactions and additional information included in section 4.8 of the harmonised SmPC. Some divergences from local SmPCs have been harmonised with acceptable justification. The information presented by the MAH was considered to be appropriate and comprehensive and as such the proposed wording is considered as acceptable by the CHMP.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.9 – Overdose

The potential for overdose use of Varilrix has not been formally studied.

The MAH monitored potential harm from overdose using routine pharmacovigilance activities; any updates are provided in Periodic Benefit-Risk Evaluation Reports.

Cases of accidental administration of more than the recommended dose of Varilrix have been reported. Amongst these cases, the following adverse events were reported: lethargy and convulsions. In the other cases reported as overdose there were no associated adverse events.

The wording proposed for the SmPC Section 4.9 Overdose in the harmonised SmPC was already approved in most countries and it is considered acceptable by CHMP.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.1 – Pharmacodynamic properties

Mechanism of action

The harmonised wording for the mechanism of action was already approved in most of the national SmPCs:

"Varilrix produces an attenuated clinically inapparent varicella infection in susceptible subjects".

This statement is to be followed by:

"The presence of antibodies is accepted as evidence of protection, however, there is no established limit of protection for varicella disease."

as approved in the Greek SmPC (but placed in the immune response subsection).

The combination of both sentences is endorsed by CHMP.

Of note, Spain had a different wording mentioning the cellular and humoral immune response, and how the Oka strain was obtained and attenuated. CHMP considered that this information was not relevant in order to describe the mechanism of action and as such, it has not been included in the harmonised SmPC.

Pharmacodynamic effects

Efficacy and effectiveness

Efficacy of Varilrix against varicella disease was evaluated in study OKA-H-179 and its extension studies, OKA-H-180, 181, and 182, for a 10-year follow-up period. The study has been completed and the efficacy data during the 10-year follow-up period were included in a Type II variation to update the national V SmPCs accordingly (referred to as V OKA-H-182 Year 10 (Y10) variation). The proposed harmonised SmPC wording for this section is a compilation of optimal wording from the different SmPCs.

The wording for the effectiveness data provided in the harmonised SmPC is:

"Effectiveness data, deriving from observation in different contexts (epidemic onset, case-control studies, observational studies, databases, models) suggest a higher level of protection and a decrease in the occurrence of cases of chickenpox following two doses of vaccine compared to a single dose.

The impact of one dose of Varilrix in reducing varicella hospitalisations and ambulatory visits among children were respectively 81% and 87% overall."

The first paragraph is the wording of the currently approved IT SmPC, after assessment of the V OKA-H-182 Y10 variation.

The second paragraph is based on a publication [Quian, 2008²²] during the national OKA-H-182 Y2 variation.

Post-Exposure Prophylaxis

The harmonised wording for this section is identical to the one already approved in some national SmPCs and it was endorsed by CHMP. The supportive data is already discussed in section 4.1.

Immune response after subcutaneous administration

Healthy individuals

The wording for this subsection in the harmonised SmPC is:

"In children aged 11 months to 21 months the seroresponse rate, when measured by ELISA 6 weeks after vaccination, was 89.6% after one vaccine dose and 100% after the second vaccine dose.

In children aged 9 months to 12 years the overall seroconversion rate, when measured by Immunofluorescence Assay (IFA) 6 weeks after vaccination, was >98% after one vaccine dose.

In children aged 9 months to 6 years the seroconversion rate, when measured by IFA 6 weeks after vaccination, was 100% after a second vaccine dose. A marked increase of antibody titres was observed following the administration of a second dose (5 to 26-fold increase of geometric mean titres).

In subjects aged 13 years and above the seroconversion rate, when measured by IFA 6 weeks after vaccination, was 100% after the second vaccine dose. One year after vaccination, all subjects tested were still seropositive".

The first paragraph represents the data of study OKA-H-186, which was designed to evaluate the immunogenicity and safety of 2 doses of HSA-containing vs. HSA-free Varilrix formulations. In this study, the immune response to VZV was measured by enzyme-linked immunosorbent assay (ELISA), and the results in the HSA-containing treatment arm are provided to align with the Varilrix formulation used in the other studies provided in the immunogenicity subsection of the proposed V Art 30 SmPC.

The second paragraph represents the pooled immunogenicity results when measured by immunofluorescence assay (IFA) of 10 pivotal studies included in the initial file for registration of Varilrix (a total of 1409 subjects in studies OKA-H-024, 026, 028, 030, 031, 032, 035 and 038 in 9-36 months of age, OKA-H-033 in 5-6 years of age and OKAH- 034 in 12-13 years of age) in which subjects received one dose of HSA-containing Varilrix formulation.

The third paragraph represents the pooled immunogenicity results when measured by IFA of 3 studies (a total of 483 subjects in studies MMRV-018 in 9-10 months of age, and MMRV-046 and MMRV-047 in 13 to 83 months of age) in which subjects received 2 doses of HSA-containing Varilrix formulation within a time interval of 6 weeks to 3 months.

The fourth paragraph represents the immunogenicity results when measured by IFA of 8 studies (OKA-H-039, 040, 043, 134, 136, 137, 145 and 170) in which subjects aged 1-60 years received 2 doses of HSA-containing Varilrix formulation within a time interval of 4 to 12 weeks.

The harmonised wording is similar to the one already included in the national SmPCs and is endorsed by CHMP.

²² Quian J, Rüttimann R, Romero C, Dall'Orso P, Cerisola A, Breuer T, Greenberg M, Verstraeten T. Impact of universal varicella vaccination on 1-year-olds in Uruguay: 1997-2005. Arch Dis Child. 2008 Oct;93(10):845-50. doi: 10.1136/adc.2007.126243. Epub 2008 May 2. PMID: 18456699; PMCID: PMC2563416.

Individuals at high risk of severe varicella

Considering all studies, including studies with the currently used refrigerator-stable Varilrix formulation, the MAH proposed to include a more generic wording in the harmonised SmPC to cover all currently available data. The modified wording is considered acceptable by CHMP.

Some additional wording included in some national SmPCs, were not included in the harmonised SmPC, as CHMP considered that, it did not provide valuable information for healthcare professionals, were already covered in other sections of the SmPC or were no longer relevant.

Immune response after intramuscular administration

With inclusion of IM administration in the harmonised SmPC (previously only approved in Germany), the MAH proposed to add the immunogenicity conclusion of the supporting study (MMRV-048) under the subtitle "Immune response after intramuscular administration".

The wording for this additional subsection in the harmonised SmPC is:

"The immunogenicity of Varilrix administered intramuscularly is based on a comparative study where 283 healthy children aged 11 to 21 months received GSK's combined measles, mumps, rubella and varicella vaccine (containing the same varicella strain as Varilrix) either by subcutaneous or intramuscular route. Comparable immunogenicity was demonstrated for both administration routes."

The MAH proposed to slightly amend the wording on IM administration in the immune response section of the German SmPC in order to only take into account the subjects included in the immunogenicity analysis (i.e. 283 subjects in the ATP cohort for immunogenicity) and to add the age of the subjects in study MMRV-048.

The harmonised wording was considered to be acceptable by CHMP.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.2 – Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.3 – Preclinical safety data

Varilrix vaccine is a lyophilized preparation of the attenuated OKA strain obtained by propagation in MRC5 human diploid cells and is indicated for active immunisation against varicella.

Varilrix vaccine was first approved in Europe in 1994, before the EMEA *Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines* came into force in 1998. Consequently, GLP toxicity studies have not been performed with Varilrix vaccine. However, tests for the varicella working seed have been conducted in animals as well general safety tests in accordance with the Ph. Eur. and WHO requirements.

The wording for the SmPC Section 5.3 Preclinical safety data in the harmonised SmPC is:

"Non-clinical data reveal no special hazard for humans based on general safety tests performed in animals",

as already approved in some national SmPCs.

CHMP considered the wording to be acceptable.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Package Leaflet (PL)

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

3. Recommendation

Based on the review of all available data the CHMP recommended the revision and harmonisation of the product information for Varilrix and associated names. The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

4. Grounds for 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.