# Adjupanrix

## Procedural steps taken and scientific information after the authorisation

| Application number | Scope | Opinion/ Notification [1] issued on | Commission Decision Issued [2] / amended on | Product Information affected [3] | Summary |
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| IB/0077 | B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation | 01/06/2022 | n/a | | |
| II/0074 | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or | 22/04/2022 | 24/05/2022 | SmPC, Labelling and | Please refer to Scientific Discussion Adjupanrix-H-C-1206- |

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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| | modification of an approved one | | | PL | II-74 |
| IB/0078/G | This was an application for a group of variations.<br><br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation<br>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 22/04/2022 | n/a | | |
| IA/0076/G | This was an application for a group of variations.<br><br>B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material<br>B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 11/02/2022 | n/a | | |
| PSUSA/2281/202105 | Periodic Safety Update EU Single assessment - pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) | 13/01/2022 | n/a | | PRAC Recommendation - maintenance |

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| IA/0073/G | This was an application for a group of variations.<br><br>B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>A.7 - Administrative change - Deletion of manufacturing sites | 04/03/2021 | n/a | | |
| II/0072/G | This was an application for a group of variations.<br><br>A grouped application of 3 type II variations under category C.I.13:<br>- Submission of a safety pharmacology study performed to assess the effect of AS03 alone and the adjuvanted influenza antigen on cardiovascular and respiratory of telemetered dogs (study MDS AA80120).<br>- Submission of a biodistribution study (study GSK-CH-02-11) conducted in mice with the 3 components of the AS03 Adjuvant System radio-labelled ([14C]-α-tocopherol, [14C]-squalene, and [3H]-polysorbate) to support the understanding of mode of action of AS03.<br>- Submission of a GLP reproductive and developmental toxicity study (study HLS GVB/007/063710) conducted to evaluate the effect of AS03 on embryo-fetal and peri- and post-natal development in Crl:CD® (SD) IGS BR rats following intramuscular administration. | 04/02/2021 | n/a | | |

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| | C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | | | | |
| PSUSA/2281/ 202005 | Periodic Safety Update EU Single assessment - pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) | 14/01/2021 | n/a | | PRAC Recommendation - maintenance |
| IAIN/0071/G | This was an application for a group of variations.<br><br>B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale<br>A.7 - Administrative change - Deletion of manufacturing sites | 26/11/2020 | n/a | | |
| PSUSA/2281/ 201905 | Periodic Safety Update EU Single assessment - pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) | 28/11/2019 | n/a | | PRAC Recommendation - maintenance |
| R/0062 | Renewal of the marketing authorisation. | 29/05/2019 | 31/07/2019 | | Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Adjupanrix in the approved indication remains favourable and therefore recommended the renewal of the marketing |

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| | | | | | authorisation with unlimited validity. |
| IA/0068 | B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits | 29/07/2019 | n/a | | |
| IA/0067/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.II.c.2.b - Change in test procedure for an excipient - Deletion of a test procedure if an alternative test procedure is already authorised | 26/07/2019 | n/a | | |
| WS/1670 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.II.z - Quality change - Finished product - Other variation | 25/07/2019 | n/a | | |
| IG/1110 | A.7 - Administrative change - Deletion of manufacturing sites | 12/07/2019 | n/a | | |
| IB/0064 | B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process | 05/07/2019 | n/a | | |
| IG/1096 | A.7 - Administrative change - Deletion of manufacturing sites | 29/05/2019 | n/a | | |

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| IB/0061/G | This was an application for a group of variations.<br><br>B.I.z - Quality change - Active substance - Other variation<br>B.I.z - Quality change - Active substance - Other variation<br>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits | 29/11/2018 | n/a | | |
| PSUSA/2281/201805 | Periodic Safety Update EU Single assessment - pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) | 29/11/2018 | n/a | | PRAC Recommendation - maintenance |
| IB/0060 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 21/09/2018 | 31/07/2019 | SmPC, Annex II, Labelling and PL | |
| II/0058/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes<br>B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological | 25/05/2018 | n/a | | |

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| | medicinal product in accordance with an approved stability protocol<br>B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method | | | | |
| PSUSA/2281/ 201705 | Periodic Safety Update EU Single assessment - pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) | 30/11/2017 | n/a | | Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Prepandrix in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. |
| IB/0057 | B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol | 23/11/2017 | n/a | | |
| IA/0055 | A.7 - Administrative change - Deletion of manufacturing sites | 30/06/2017 | n/a | | |
| IB/0054/G | This was an application for a group of variations.<br><br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation<br>B.I.b.z - Change in control of the AS - Other variation<br>B.II.a.z - Change in description and composition of the Finished Product - Other variation<br>B.II.a.z - Change in description and composition of | 08/03/2017 | n/a | | |

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| | the Finished Product - Other variation<br>B.II.b.z - Change in manufacture of the Finished Product - Other variation<br>B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation<br>B.II.c.z - Change in control of excipients in the Finished Product - Other variation<br>B.II.d.z - Change in control of the Finished Product - Other variation<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | | | | |
| PSUSA/2281/ 201605 | Periodic Safety Update EU Single assessment - pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) | 01/12/2016 | n/a | | PRAC Recommendation - maintenance |
| IG/0717 | B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 01/09/2016 | n/a | | |
| IA/0052/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites | 24/08/2016 | n/a | | |

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| | B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits<br>B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation | | | | |
| IG/0679 | B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method | 01/06/2016 | n/a | | |
| IB/0048/G | This was an application for a group of variations.<br><br>B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data<br>B.I.d.1.b.1 - Stability of AS - Change in the storage conditions - Change to more restrictive storage conditions of the AS | 30/05/2016 | n/a | | |
| IG/0680 | B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method | 27/05/2016 | n/a | | |
| IB/0046 | B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved | 06/01/2016 | n/a | | |

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| | stability protocol | | | | |
| N/0047 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 14/12/2015 | 31/07/2019 | PL | |
| PSUSA/2281/ 201505 | Periodic Safety Update EU Single assessment - pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) | 03/12/2015 | n/a | | PRAC Recommendation - maintenance |
| IB/0044 | B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | 29/07/2015 | n/a | | |
| IB/0043/G | This was an application for a group of variations.<br><br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation<br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation<br>B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer | 29/04/2015 | n/a | | |
| IB/0042/G | This was an application for a group of variations.<br><br>B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation<br>B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non- | 14/01/2015 | n/a | | |

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| | significant specification parameter (e.g. deletion of an obsolete parameter) | | | | |
| PSUV/0040 | Periodic Safety Update | 04/12/2014 | n/a | | PRAC Recommendation - maintenance |
| IG/0498 | B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised | 21/11/2014 | n/a | | |
| IG/0467 | B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 20/08/2014 | n/a | | |
| IG/0466/G | This was an application for a group of variations.<br><br>B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 20/08/2014 | n/a | | |
| R/0036 | Renewal of the marketing authorisation. | 22/05/2014 | 18/07/2014 | | Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP |

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| | | | | | considers that the benefit-risk balance of Adjupanrix remains positive, but considers that its safety profile is to be closely monitored for the following reasons:<br>Considering the theoretical possibility that the AS03 adjuvant or some other vaccine component common to the MAH's pandemic influenza vaccines has a role in the development of narcolepsy, this event is considered a potential risk for Adjupanrix until data awaited from epidemiological and mechanistic studies allow for further discussion on whether this risk may be applied to AS03-containing products other than Pandemrix H1N1.<br>The CHMP decided that the MAH should continue to submit 1-yearly PSURs.<br>Therefore, based upon the safety profile of Adjupanrix, which requires the submission of 1-yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years' time. |
| II/0034 | Update of section 4.4 of the SmPC in order to add a warning regarding the observed increased risk of narcolepsy following vaccination with Pandemrix, the MAH's ASO3 adjuvanted H1N1 influenza vaccine, based on a review of epidemiologic or post-marketing surveillance. Furthermore, the PI is being brought in line with the latest QRD template version 9.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 26/06/2014 | 11/06/2015 | SmPC, Annex II and PL | Epidemiological studies relating to another AS03-adjuvanted vaccine (Pandemrix H1N1, also manufactured in the same facility as Adjupanrix), in several European countries have indicated an increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated individuals. In children/adolescents (aged up to 20 years), these studies have indicated an additional 1.4 to 8 cases in 100,000 vaccinated subjects. Available epidemiological data in adults aged over 20 years have indicated approximately 1 additional case per 100,000 vaccinated subjects. These data suggest that the excess risk tends to decline with increasing age at vaccination.<br>There is currently no evidence to indicate that Adjupanrix |

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| | | | | | may be associated with a risk of narcolepsy. |
| IG/0446 | C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location | 24/06/2014 | n/a | | |
| II/0035/G | This was an application for a group of variations.<br><br>Update of sections 4.2 and 5.1 of the SmPC in order to extend up to 12 months the interval between the two doses based on data from study D-PAN-H5N1-012 in adults. In addition some corrections to figures included in section 5.1 of the SmPC were introduced. The Package Leaflet is updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 20/03/2014 | 22/05/2014 | SmPC and PL | The data assessed in this group of variations comprise additional efficacy and safety data from adult subjects in Study 012 who received A/Vietnam and were subsequently boosted with A/Vietnam or A/Indonesia at 6 or 12 months. The immune response achieved with boosting at 12 months was comparable to that achieved with boosting at 6 months. This applies to both single and double priming regimens, and cross-protection for heterologous strains. There was no evidence of a waning of the priming effect over the 12 month period. The safety data support the favourable benefit-risk relationship for the regimens studied. The amendments proposed for the SmPC and PL were agreed. |
| IB/0033/G | This was an application for a group of variations.<br><br>B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol<br>B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol | 06/03/2014 | 22/05/2014 | SmPC and PL | |

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| | B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation | | | | |
| PSUV/0032 | Periodic Safety Update | 18/12/2013 | 28/02/2014 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0032. |
| IG/0306 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 12/06/2013 | n/a | | |
| IG/0297 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 19/04/2013 | n/a | | |
| IG/0265/G | This was an application for a group of variations.<br><br>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | 28/01/2013 | n/a | | |
| IB/0027/G | This was an application for a group of variations.<br><br>B.I.a.1.z - Change in the manufacturer of AS or of a | 10/09/2012 | n/a | | |

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| | starting material/reagent/intermediate for AS - Other variation<br>A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS | | | | |
| IB/0026 | B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | 24/08/2012 | n/a | | |
| IAIN/0025 | A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs | 15/06/2012 | 31/10/2012 | SmPC, Labelling and PL | |
| IB/0023/G | This was an application for a group of variations.<br><br>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation<br>A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS | 17/04/2012 | n/a | | |
| IA/0024 | A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) | 26/03/2012 | n/a | | |
| II/0014 | Shelf-Life extension of active substance | 19/01/2012 | 19/01/2012 | | |

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| | B.I.d.1.a.3 - Stability of AS - Change in the re-test period/storage period - Extension of storage period of a biological/immunological AS not in accordance with an approved stability protocol | | | | |
| IB/0012/G | This was an application for a group of variations.<br><br>B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation<br>B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>A.7 - Administrative change - Deletion of manufacturing sites | 13/01/2012 | n/a | | |
| WS/0161/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Type II: to update sections 4.6 and 4.8 of the SmPC, with data on experience gained with Pandemrix, as requested by the CHMP in the 4th PSUR assessment for the AS03-adjuvanted H5N1 vaccine Marketing Authorisations. The PL is updated | 17/11/2011 | 22/12/2011 | | The proposed changes to the Product Information, to reflect post marketing experience with Pandemrix in SmPC sections 4.6 and 4.8, and to align the Product Information with wording in the Pandemrix and Pumarix Product Informations were considered acceptable. Wording for SmPC section 6.6 (Special precautions for disposal and other handling) in the paragraphs in points 1 and 7 of 'Instructions for mixing and administration of the vaccine were further revised to add more clarity. |

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| | accordingly.<br>1st Type IB: to align the SmPC, labelling and PL texts for Prepandrix and Pandemic duplicate H5N1 licences, with wording present in the Pandemrix and Pumarix PI's.<br>2nd Type IB: to align the PL text for Prepandrix and Pandemic duplicate H5N1 licences with wording present in the Arepanrix and Pumarix PLs following readability testing.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation<br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data<br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | | | | |
| WS/0153 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC to include a warning on psychogenic syncope based on the available safety data. The PL was proposed to be updated in accordance. In addition, the company took the opportunity to update the list of local representatives in the PL of Pumarix, Ambirix, | 17/11/2011 | 22/12/2011 | SmPC and PL | Based on a review of literature and a search in the global safety database performed by the MAH, the CHMP recommended including a wording on psychogenic syncope to the product information of the MAH injectable vaccines. The literature review showed an incidence peak occurred around the age of 15 years, with females having more than twice the incidence of males. The syncope reports with secondary injuries were reported most frequently in children and adolescents.<br>Given that psychogenic syncope is not a true side effect, it was not considered appropriate to include syncope as an undesirable effect in section 4.8 of the SmPC. However, as such events can result in injury, and may not have |

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| | Pandemrix, Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals, Prepandrix and Fendrix.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | occurred in the absence of the vaccination, the CHMP recommended to add a reference to such events in section 4.4 'Warning and Precaution' of the SmPC and in the PL. |
| IG/0133 | C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | 22/11/2011 | n/a | | |
| II/0011 | Update of section 5.1 'Pharmacodynamic Properties' of the SmPC to include persistence/booster data from<br>- Study H5N1-009/022/023 (conducted in children 3-9 years of age): Persistence Month 24<br>- Study H5N1-002/030/038 (conducted in adults 18-60 years of age): Persistence Month 36 & Booster given at Month 36<br>- Study H5N1-010 (in adults over 60 years of age): Persistence Month 24<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 20/10/2011 | 22/11/2011 | SmPC | Immunogenicity and safety data at month 24 and 36 (including booster) were considered to be in line with the cumulative experience of the AS03-adjuvanted vaccines. There are no new concerns in view of immunogenicity and the reflection of the longer-term data from these studies in the SmPC was considered appropriate.<br>In view of safety, no new concerns have arisen from these data that would require an update of the Product Information at this stage. |
| IA/0015/G | This was an application for a group of variations.<br><br>B.II.e.2.c - Change in the specification parameters | 11/11/2011 | n/a | | |

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| | and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method | | | | |
| IA/0013/G | This was an application for a group of variations.<br><br>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter<br>B.II.d.1.b - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits for medicinal products subject to Official Batch Release | 25/10/2011 | n/a | | |
| IB/0009 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 11/08/2011 | n/a | SmPC, Labelling and PL | |
| IA/0010 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test | 05/08/2011 | n/a | | |

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| | procedure | | | | |
| IB/0008 | B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation | 08/07/2011 | n/a | | |
| IG/0081 | C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV | 07/07/2011 | n/a | | |
| II/0006/G | This was an application for a group of variations.<br><br>- Additional site for the manufacturing of the adjuvant.<br>- Additional site for the filling of the adjuvant.<br>- Additional site for the QC testing of the adjuvant.<br>- Extension of the shelf-life of the adjuvant.<br>- Additional container and alternative storage temperature for the long-term storage and/or transport of the adjuvant bulks.<br>- Changes to the QC testing of the adjuvant.<br><br>B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.<br>B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol | 23/06/2011 | 23/06/2011 | | |

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| | B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place<br>B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method<br>B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.<br>B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products<br>B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product<br>B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product<br>B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product<br>B.II.b.5.d - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of an in-process test which may | | | | |

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| | have a significant effect on the overall quality of the finished product<br>B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits | | | | |
| II/0005/G | This was an application for a group of variations.<br><br>- Addition of a building to allow increased production capacity of the H5N1 monvalent bulk.<br>- Introduction of minor modifications in the methodology for testing of the HA content for the viral seeds, monovalent bulks, final bulks and final containers.<br>- Alternative container for the transport and storage of H5N1 antigen final bulk.<br>- Additional site for the filling, labelling, pre-packaging operation and quality control testing of the antigen component of the AS03 adjuvanted H5N1 vaccine.<br><br>B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product<br>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate | 23/06/2011 | 23/06/2011 | | |

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| | B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products<br>B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs<br>B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.<br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place | | | | |
| IA/0007 | B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site | 11/05/2011 | n/a | | |
| IG/0062/G | This was an application for a group of variations.<br><br>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the | 27/04/2011 | n/a | | |

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| | DD<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | | | | |
| II/0004 | To reflect new data obtained from study D-Pan H5N1-009 in section 4.2, 4.4, 4.8 and 5.1 of the SmPC, as well as in the Package Leaflet (sections 3 and 4). This clinical study is conducted in children aged 3 to 9 years, to evaluate the immunogenicity, reactogenicity and safety of three formulations of AS03 adjuvanted H5N1 vaccine, given following a two dose schedule on Days 0 and 21. The MAH is also taking the opportunity of this procedure to update Annex II in order to reflect the wording on the Pharmacovigilance System as requested by CHMP and to include the Marketing Authorisation numbers in the Labelling.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 17/03/2011 | 18/04/2011 | SmPC, Annex II, Labelling and PL | Concerning immune response, the D42 HI immune response parameters (SCR, SPR, SCF) did not clearly distinguish any one of the three formulations (Half HA/Half AS03, Full HA/Half AS03, Full HA/Full AS03) tested. However, the administration of a higher HA dose and, especially, the full adult dose, demonstrated advantages in terms of several HI and NA immune parameters. In particular, use of the adult dose gave improved HI responses to the heterologous strain and higher NA GMTs.<br>Concerning safety, the greatest differences between the H5N1 vaccine and control groups in this study were seen when the adult dose was administered. Despite the greater local and general reactogenicity with the adult dose uptake of the second dose was very high and only four subjects did not complete both doses in the entire study. In addition the data do not indicate that higher reactogenicity was associated with SAEs.<br>Overall, a difference in the frequency of adverse reactions between half adult and adult doses was observed after each dose. However, the administration of a second half adult or an adult dose did not enhance the reactogenicity, except for rates of general symptoms which were higher after the second adult dose. |
| IA/0003 | B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of | 16/12/2010 | n/a | | |

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| | specification limits | | | | |
| IB/0002 | To extend the shelf life of the finished product from 24 months to 36 months at 2-8 degrees.<br>To change in the specification limits for squalene from "not more than 20 ppm" to "not more than 10ppm".<br><br>B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol | 16/07/2010 | n/a | | |
| IB/0001 | B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data | 23/06/2010 | n/a | | |