PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for *Adjupanrix* (Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted))

This is a summary of the risk management plan (RMP) for *Adjupanrix*. The RMP details important risks of *Adjupanrix*, how these risks can be minimised, and how more information will be obtained about *Adjupanrix* 's risks and uncertainties (missing information).

Adjupanrix's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *Adjupanrix* should be used.

This summary of the RMP for *Adjupanrix* should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of *Adjupanrix*'s RMP.

I. The medicine and what it is used for

Adjupanrix is authorised for prophylaxis of influenza in an officially declared pandemic situation. (see SmPC for the full indication). It contains Pandemic Influenza Vaccine (H5N1) (Split Virion, inactivated, adjuvanted) as the active substance and it is given by intramuscular injection.
Further information about the evaluation of *Adjupanrix*'s benefits can be found in *Adjupanrix's* EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

'internet site'.ema.europa.eu/en/medicines/human/EPAR/adjupanrix-previously-pandemic-influenza-vaccine-h5n1-split-virion-inactivated-adjuvanted

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of *Adjupanrix*, together with measures to minimise such risks and the proposed studies for learning more about *Adjupanrix*'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of *Adjupanrix*, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessmentso that immediate action can be taken as necessary. These measures constitute *routine PhV activities*.

If important information that may affect the safe use of *Adjupanrix* is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of *Adjupanrix* are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of *Adjupanrix*. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	Anaphylaxis Autoimmune hepatitis Bell's palsy Convulsion Demyelinating disorders Encephalitis Guillain-Barre Syndrome Increased concentration of hepatic enzymes

	Narcolepsy Neuritis Vasculitis
Missing information	Safety in pregnant women Safety in patients with severe underlying disease, including immunocompromise

Since the last RMP for *Adjupanrix* was published, the risk of solid organ transplant rejection has been removed with agreement from the CHMP, based on the results of an epidemiological study which found no increased risk of solid organ transplant rejection following vaccination with *Adjupanrix.* Several other risks were also removed including fever, vaccination failure/effectiveness, medical errors/misidentification of vaccine, contamination of multidose vials and coring of the rubber stopper on the antigen vial. These were removed as they were deemed to be either adequately addressed by the product information included with the vaccine, or they were not considered significant safety concerns.

II.B Summary of important risks

Table 2 Summary of important risks

Autoimmune hepatitis	
Evidence for linking the risk to the medicine	Two reported cases of AIH were received from GSK clinical trials of H5N1+AS03 vaccines. One report, concerning a female child, 3.5 years of age, was received from a clinical trial using the A/Vietnam/1194/2004 strain and was determined to be an exacerbation of a pre-existing condition. The second report, concerning an adult male, 29 years of age, was received from a clinical trial using the A/Indonesia/5/2005 strain; a liver biopsy showed a mild, chronic hepatitis compatible with AIH, baseline values of transaminases were not available. No signal for AIH was identified during post-marketing use of GSK's AS03-adjuvanted H1N1 pandemic influenza vaccines. No events were reported for the doses of D-Pan H5N1 AS03 adjuvanted vaccines administered for 78 personnel deemed at risk.
Risk factors and risk groups	None known; AIH occurs in persons of all ages, sexes, and races [Hennes , 2008]. In the absence of definitive biological and epidemiological data, Tavares Da Silva, et al. proposed one year as the maximum, reasonable theoretical risk interval for incident potential immune-mediated diseases [Tavares Da Silva , 2013].
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: Targeted Follow-Up Questionnaire

Additional PhV activities	Safety surveillance study of real world use

Bell's palsy	
Evidence for linking the risk to the medicine	The incidence rate is not well established. Rates in the literature range from 13 to 43/100,000 person-years. Cumulatively, one SAE of Bell's Palsy (LLT)/Facial Paralysis (PT) was reported in GSK's H5N1 clinical trials.
Risk factors and risk groups	Bell's palsy can affect all age groups and genders. There are no known background factors that alter an individual's risk for developing Bell's palsy. Most cases are idiopathic. Known associations with HIV infection, Lyme disease, sarcoidosis, Sjögren's syndrome, acute otitis media, tumour, hypertension, diabetes mellitus, and trauma. Pregnancy and certain viral illnesses (especially herpes viruses) can also be associated with Bell's palsy [Greco , 2012].
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: Targeted Follow-Up Questionnaire
Additional PhV activities	Additional PhV activities: Safety surveillance study of real world use

Convulsion	
Evidence for linking the risk to the medicine	Febrile seizures are the most common type of non-epileptic seizures observed after vaccination. Approximately 3% to 4% of all typically-developing children aged 3 months through 6 years will have at least one febrile seizure [Bonhoeffer , 2004].In clinical studies of H5N1 adjuvanted vaccine, there have been 7 SAEs of febrile convulsion reported in 4 subjects associated with fever in children. Four SAEs of seizure were reported in clinical studies of H5N1 adjuvanted vaccines, none was considered related to the vaccine. To date, there are no cumulative spontaneous or post-marketing reports as *Adjupanrix* has not been commercially launched
Risk factors and risk groups	Age 3 months through 6 years, with peak incidence at 9-20 months of age [Cross , 2012]. Genetic susceptibility; siblings have a 25% risk [Cross , 2012].

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 and PIL Section 4 Additional risk minimisation measures: Targeted Follow-Up Questionnaire
Additional PhV activities	Additional PhV activities: Safety surveillance study of real world use

Demyelinating disorders	
Evidence for linking the risk to the medicine	Varies with type of disorder. The most common type, Multiple Sclerosis, varies markedly geographically, from below 5/100 000 in many areas of Africa, South America and Asia, to over 100/100 000 in Scotland and parts of Scandinavia and Canada [Love , 2006]. A GSK-supported study of *Arepanrix* H1N1 (EPI-FLU-010 (Swedish PASS)) found no evidence of an association between vaccination with and the incidence of MS or of other CNS demyelinating conditions. In clinical studies with GSK's H5N1 pandemic influenza vaccine, 2 cases of demyelination were reported. MS of new onset was reported in a 38-year-old subject 1 year after vaccination, and one case of optic neuritis was reported in a 21-year-old subject, 943 days after the second dose of vaccine, which resolved with treatment.
Risk factors and risk groups	none
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 Additional risk minimisation measures: Targeted Follow-Up Questionnaire
Additional PhV activities	Additional PhV activities: Safety surveillance study of real world use

Encephalitis

Evidence for linking the risk to the medicine	The term encompasses several disorders, infectious and non-infectious in nature; as well as acute and chronic. Rates of viral encephalitis in the literature range from <1 to 7/100,000 [Sejvar , 2007], with an incidence of 3.5 and 7.4 per 100,000 patient-years [Granerod , 2007]. A multicentre population-based prospective study found that 21% of subjects with acute encephalitis had an immune-mediated etiology; and 38% of those had anti-neuronal antibodies present [Armangue , 2014]. Cumulatively, no SAEs related to encephalitis were reported in clinical trials of GSK H5N1 adjuvanted vaccines.
Risk factors and risk groups	Possibly geographical proximity to endemic disease vectors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 Additional risk minimisation measures: Targeted Follow-Up Questionnaire
Additional PhV activities	Additional PhV activities: Safety surveillance study of real world use

Guillain-Barre Syndrome	
Evidence for linking the risk to the medicine	The annual incidence of GBS in the general population has been estimated to be 1 to 2 per 100,000 [Sejvar , 2011]. It has been estimated that seasonal influenza vaccines are associated with approximately 1 excess case per million persons vaccinated [CDC, 2010]. Cumulatively, no SAEs related to GBS were reported in clinical trials of GSK's H5N1 adjuvanted vaccine. Spontaneous reports of GBS have been received following vaccination with GSK's H1N1 adjuvanted vaccine); however, a causal association between vaccination and GBS has not been established. Data from a post-marketing epidemiological study in Canada indicate a small but significant increased relative risk of GBS of 1.80 (95% CI, 1.63-4.62) in the 56-day period following vaccination with *Arepanrix* H1N1 (in persons 50 years of age and older). The number of GBS cases attributable to vaccination was approximately 2 per 1 million doses.
Risk factors and risk groups	Slight male predominance, with a ratio of men to women of 1.78 [95% CI, 1.36-2.33]. Two-thirds of cases have a history of episodes of gastrointestinal or upper respiratory infections 3 days to 6 weeks before onset. CMV and *Campylobacter jejuni* infections have been implicated in up to 10% and 30% of cases, respectively. Epstein-Barr, varicella-zoster and mycoplasma pneumonia infections have also been associated with GBS syndrome [Yuki , 2012]. The incidence rises through the first 20 years of life and is stable again until the 7th decade, when the incidence is highest, and morbidity greatest
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 Additional risk minimisation measures: Targeted Follow-Up Questionnaire

Additional PhV activities	Additional PhV activities: Safety surveillance study of real world use

Increased concentrations of hepatic enzymes	
Evidence for linking the risk to the medicine	Abnormal elevations of serum liver chemistries may occur in 1% to 4% of the asymptomatic population. There are numerous causes of increased concentrations of transaminases [AGACPC, 2002]. Five cases in 4 patients involving increased concentrations of hepatic enzymes following vaccination with GSK's AS03-adjuvanted H5N1 vaccine have been reported from clinical trials. Two cases were from the same patient who was initially thought to have Burkitt's lymphoma, whose disease progressed to multi-organ failure. One case of drug-induced liver injury occurred in another subject 9 months after the second dose of H5N1 vaccine. A subsequent positive rechallenge with nitrofurantoin was considered causal. Two other cases were of autoimmune hepatitis. Both subjects were subsequently found to have evidence of hepatic disease preceding vaccination. There is no evidence from clinical trial data of a direct hepatotoxic effect of the AS03-adjuvanted H5N1 vaccine. Abnormal elevations of serum liver chemistries may occur in 1% to 4% of the asymptomatic population. Increased concentrations of hepatic enzymes are closely monitored by GSK as part of the close monitoring for AIH.
Risk factors and risk groups	Concentrations of transaminases may be increased due to infections, alcohol consumption, drugs, strenuous exercise, steatosis, and many chronic medical conditions [AGACPC, 2002].
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: Targeted Follow-Up Questionnaire
Additional PhV activities	Additional PhV activities: Safety surveillance study of real world use

Narcolepsy	
Evidence for linking the risk to the medicine	Studies from Europe found an increase in relative risk of narcolepsy, in those vaccinated withH1N1 *Pandemrix* compared to those unvaccinated, in the population under 20 years of age. The relative risk (RR) estimates ranged from 1.6 to 14.4, and the CI varied widely, from 0.3 to 48.5 The values translated into an absolute attributable risk of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents, and approximately 1 additional case per 100,000 vaccinated adults. [Sturkenboom , 2015]. Narcolepsy affects approximately 0.02% of the population worldwide [Mahlios , 2013]. The overall pooled incidence rate in Europe is 0.93 per 100,000 person-years (95% CI, 0.90 –

	0.97). A major peak occurs in persons 15 to 30 years of age, with a less pronounced peak at 60 years of age [Wijnans , 2013]. In a US study, which stratified the incident rate by age and gender, the rate of narcolepsy per 100,000-person years was 1.37 (1.72 for men and 1.05 for women) and was found to be highest in the 2nd decade, followed in descending order by the 3rd, 4th and 1st decades [Sha ,2016;Silber Silber , 2002]. Narcolepsy has not been reported in any subject in a GSK clinical study with pandemic influenza H5N1 vaccine.
Risk factors and risk groups	Narcolepsy with cataplexy is linked with genetic susceptibility factors such as HLA DQB1*0602, frequently in combination with HLA DRB1*15:01 [Mahlios , 2013]. Other reported immunological associations include polymorphisms in the T cell receptor alpha locus, in Cathepsin H, an enzyme expressed in antigen presenting cells and within the tumour necrosis factor ligand superfamily OX40L [Mahlios 2013].
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: Targeted Follow-Up Questionnaire
Additional PhV activities	Additional PhV activities: Safety surveillance study of real world use

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

A post-authorisation cohort study examining real world use, that will be conducted during a pandemic.

II.C.2 Other studies in post-authorisation development plan

There are no additional studies planned for *Adjupanrix*

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