

MAH:

PaxVax Berna GmbH
Oberriedstrasse 68
CH-3174 Thörishaus

RMP - Risk Management Plan - Summary, Version 3, for

Foclivia, Injektionssuspension in einer Fertigspritze
Foclivia, Injektionssuspension in einer Durchstechflasche

Zul.-Nr. 66156
Zul.-Nr. 66161

Active ingredient: Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain: A/Vietnam/1194/2004 (H5N1)

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Foclivia is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Foclivia in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. PaxVax Berna GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Foclivia.

Thörishaus, 3.9.2018

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for adjuvanted H5N1 influenza vaccine (aH5N1 influenza vaccine), trade names Aflunov[®] and Foclivia[®]. The RMP details important risks of aH5N1 influenza vaccine, how these risks will be minimised, and how more information will be obtained about aH5N1 influenza vaccine's risks and uncertainties (missing information).

aH5N1 influenza vaccine's summary of product characteristics (SPC/SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how aH5N1 influenza vaccine should be used.

The summary of the RMP for aH5N1 influenza vaccine 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 aH5N1 influenza vaccine's RMP.

I. The medicine and what it is used for

Foclivia[®] is a *pandemic* vaccine, authorised for prophylaxis of influenza in an officially declared pandemic situation. It contains egg-derived, inactivated, purified influenza virus surface antigens: A/Vietnam/1194/2004 (H5N1) - like strain (NIBRG-14) 7.5 micrograms per 0.5ml dose. It also contains MF59 as an adjuvant. One dose of 0.5mL is given by intramuscular injection into the deltoid muscle or anterolateral thigh (depending on muscle mass), followed by a second dose of 0.5mL after an interval of at least 3 weeks.

Aflunov[®] is a *pre-pandemic* vaccine, authorised for active immunisation against H5N1 subtype of influenza A virus. It contains egg-derived, inactivated, purified influenza virus surface antigens: A/turkey/Turkey/1/05 (H5N1)-like strain (NIBRG-23) 7.5 micrograms per 0.5ml dose. It also contains MF59 as an adjuvant. One dose of 0.5mL is given by intramuscular injection into the deltoid muscle, followed by a second dose of 0.5mL after an interval of at least 3 weeks.

Prepandemic Influenza Vaccine is a *pre-pandemic* vaccine for active immunisation against H5N1 subtype of influenza A virus. The license for this vaccine in the EU expired on 29 Nov 2015, and has not been renewed.

Further information about the evaluation of aH5N1 influenza vaccine's benefits can be found in aH5N1 influenza vaccine's EPAR, including in its plain-language summary, available on the EMA website, under the following webpages:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001208/WC500049684.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002094/WC500101080.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002269/WC500101212.pdf

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

Important risks of aH5N1 influenza vaccine, together with measures to minimise such risks and the proposed studies for learning more about aH5N1 influenza vaccine's risks, are outlined below.

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

- Specific information, such as warnings and precautions, and advice on correct use, in the product label (SPC, Package Leaflet) 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including assessment in PSURs, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of aH5N1 influenza vaccine is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of aH5N1 influenza vaccine are risks that need special 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 aH5N1 influenza vaccine. 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).

List of important risks and missing information	
Important identified risks	<ul style="list-style-type: none"> • None
Important potential risks	<ul style="list-style-type: none"> • Neuritis • Convulsions • Anaphylaxis

	<ul style="list-style-type: none"> • Encephalitis • Vasculitis • Guillain-Barré syndrome • Demyelination • Bell's palsy • Immune thrombocytopenia • Vaccination failure
Missing information	<ul style="list-style-type: none"> • Use in pregnancy and lactation • Use in children

II.B Summary of important risks

Important potential risk: Neuritis	
Evidence for linking the risk to the medicine	<p>The strength of evidence is low, as there have been no observed cases from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, neuritis is considered an adverse event of special interest (AESI) (CHMP, Sep 2009), and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), with a potential rate of 0.45 neuritis cases per million influenza vaccinations (Vellozzi, 2009). The event is considered potentially serious and severe, as although the outcome of neuritis is usually good, recovery can be quite prolonged, with recovery of strength and function taking weeks to months. Some patients can experience longer periods of muscle weakness, or a slight permanent weakness (Miller, 2000). Neuritis usually requires medical treatment (e.g. steroids, analgesia, physiotherapy), may impact on patient's quality of life and/or may result in persistent or significant disability/incapacity (Debeer et al, 2008; Feinberg, 2010).</p> <p>On the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, neuritis is considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and is therefore classified as an important potential risk.</p>
Risk factors and risk groups	There is no evidence of any patient, dose-related or additive/synergistic risk factors; nor of a specific risk period, in relation to neuritis specifically attributed to influenza vaccine.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p><i>Neuritis is described in Section 4.8 Undesirable effects of the Prepandemic vaccine, Foclivia and Aflunov labels (SPC); and Section 4 of the Package Leaflet.</i></p> <p><u>Additional risk minimisation measures:</u></p> <p><i>No additional measures</i></p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p><i>PASS</i></p>

Important potential risk: Convulsions	
Evidence for linking the risk to the medicine	<p>The strength of evidence is low, as a limited number of cases of convulsions were observed from post-marketing or clinical trials. However, on the basis of evidence from scientific literature, convulsions are considered an AESI (CHMP, Sep 2009), and a rare potential pharmacological class effect of pandemic influenza vaccines</p>

	<p>(CHMP, Jul 2009), with a potential rate of 0.16 convulsion (febrile and afebrile) cases per million influenza vaccinations (Vellozzi, 2009). The event is considered potentially serious and severe, as it may impact on patient's quality of life and/or may result in emergency hospitalisation. Uncomplicated febrile convulsions in young children are generally a benign condition, and have not been found to be associated with increased mortality or later neurocognitive difficulties (Bakken et al, 2015). Acute medical treatment such as diazepam/midazolam may be used for prolonged convulsions, and analgesia can be used to relieve any fever discomfort (Sadlier, 2007). Those presenting with afebrile convulsions may also require acute medical treatment such as diazepam/midazolam. After the patient is stabilised and returns to baseline function; history, examination, and diagnostic testing may be performed to determine if the event was a seizure, the cause of the event, and any long-term follow-up or treatment required (Krumholz, 2007). It is likely the event will be an isolated incident (Krumholz, 2007).</p> <p>On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, convulsions are considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and are therefore classified as an important potential risk.</p>
Risk factors and risk groups	<p>Febrile convulsions risk factors include a fever of ≥ 38 °C; however are dependent on the seizure threshold (which can vary between patients), age, maturation, and genetic predisposition. Median age of onset of a febrile seizure is 18 months, and half of children present between 12 and 30 months. The risk interval for febrile convulsions is 0 to 1 day. There is an increase of incidence in the elderly for non-febrile seizures. There is no evidence of a specific risk period for any age group for non-febrile seizures.</p>
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> <i>Convulsions are described in Section 4.4 Special warning and precautions for use of the Foclivia and Prepandemic vaccine labels (SPC) and Section 4.8 Undesirable effects of Foclivia, Prepandemic vaccine and Aflunov labels (SPC); and Section 2 & 4 of the Package Leaflet.</i></p> <p><u>Additional risk minimisation measures:</u> <i>No additional measures</i></p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u> <i>PASS</i></p>

Important potential risk: Anaphylaxis	
Evidence for linking the risk to the medicine	<p>The strength of evidence is low, as a limited number of cases of anaphylaxis were observed from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, anaphylaxis is considered an AESI (CHMP, Sep 2009), and a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), with a potential rate of 1.4 anaphylaxis cases per million pandemic influenza vaccinations (Vellozzi, 2010). The event is considered potentially serious and severe as it is life-threatening and may result in emergency hospitalisation. Anaphylaxis is a life-threatening reaction with varied clinical presentations. Acute medical treatment is usually required in an emergency setting, with administration of adrenaline, oxygen, antihistamines, steroids and volume replacement, as required (Lieberman et al, 2005). With treatment, patients are likely to make a full recovery. In the review of the pandemic H1N1 influenza vaccination program, no deaths from anaphylaxis were reported (Vellozzi, 2010).</p> <p>On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above,</p>

	anaphylaxis is considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and is therefore classified as an important potential risk.
Risk factors and risk groups	The risk period for anaphylaxis is typically described as seconds to minutes of exposure. Most cases start within an hour of exposure, however in a minority of cases, symptoms may present up to 12 hours after exposure. Risk factors are previous exposure and sensitisation to the vaccine constituents or trace residues. Coexisting atopic disease, particularly asthma, are reportedly risk factors for anaphylaxis. Those with pre-existing allergic conditions such as atopic dermatitis may also have an increased risk of anaphylaxis (OR 2.83, 95%CI: 1.51-5.29).
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>Anaphylaxis is described in Section 4.3 Contraindications of the Prepandemic vaccine, Foclivia and Aflunov labels (SPC); Section 4.4 Special warning and precautions for use of the Prepandemic vaccine, Foclivia and Aflunov labels (SPC); and Section 4.8 Undesirable effects of the Prepandemic vaccine, Foclivia and Aflunov labels (SPC); and Section 2 & 4 of the Package Leaflet.</i> <u>Additional risk minimisation measures:</u> <i>No additional measures</i>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <i>PASS</i>

Important potential risk: Encephalitis	
Evidence for linking the risk to the medicine	The strength of evidence is low, as there have been no observed cases from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, encephalitis is considered an AESI (CHMP, Sep 2009), and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), with a potential rate of 0.12 encephalitis cases per million influenza vaccinations (Vellozzi, 2009). The event is considered potentially serious and severe, as with potential symptoms such as encephalopathy, seizures and loss of consciousness (Sejvar, 2007), and has a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity. The outcome in patients developing encephalitis may range widely, from complete recovery to persistent disability, coma or death. A proportion of patients developing encephalitis will be expected to have persistent neurological, functional, and cognitive sequelae lasting for months, years or indefinitely (Sejvar, 2007). Encephalitis requires medical treatment (e.g. steroids, immunoglobulin, plasmapheresis), generally in a hospital setting. On the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, encephalitis is considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and is therefore classified as an important potential risk.
Risk factors and risk groups	Encephalitis is found to be most common in children less than 10 years, and has a higher incidence in males. Immunocompromised patients are also at an increased risk. One study described the onset of encephalitis within 6 weeks after vaccination in 65.2% of patients, and in 50.7% within 2 weeks.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>Neurological disorders, such as encephalomyelitis, are described in Section 4.8 Undesirable effects of the Prepandemic vaccine, Focliva and Aflunov labels (SPC); and Section 4 of the Package Leaflet.</i> <u>Additional risk minimisation measures:</u>

	<i>No additional measures</i>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <i>PASS</i>

Important potential risk: Vasculitis	
Evidence for linking the risk to the medicine	The strength of evidence is low, as a limited number of cases of vasculitis were observed from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, vasculitis is considered an AESI (CHMP, Sep 2009) and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), with a potential rate of 341.8 vasculitis cases per 100,000 person-years after influenza vaccination (Gao, 2013). The event is considered potentially serious and severe, as depending on the type, the event may have a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity. The outcome of vasculitis varies substantially, depending on the vessels involved, and the extent of disease and/or organ involvement. There may be only transient cutaneous lesions (Lotti, 1998) or systemic vasculitides that can be life-threatening (Schattner, 2005). For those with cutaneous lesions only, spontaneous resolution is possible (Zanoni, 2016). Systemic vasculitides generally require critical medical treatment (e.g. steroids/immunosuppressants, immunoglobulin) (Woerner, 2017). On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, vasculitis is considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and is therefore classified as an important potential risk.
Risk factors and risk groups	The condition is more commonly reported in elderly; however, this could be more reflective of the target population for influenza vaccine. A medical history of underlying autoimmune disorder may play a role in risk. There is no evidence of a specific risk period.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>Vasculitis is described in Section 4.8 Undesirable effects of the Prepandemic vaccine, Focliva and Aflunov labels (SPC); and Section 4 of the Package Leaflet.</i> <u>Additional risk minimisation measures:</u> <i>No additional measures</i>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <i>PASS</i>

Important potential risk: Guillain-Barré syndrome	
Evidence for linking the risk to the medicine	The strength of evidence is low, as there have been no observed cases from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, Guillain-Barré syndrome (GBS) is considered an AESI (CHMP, Sep 2009), and a very rare potential pharmacological class effect of pandemic influenza vaccines. (CHMP, Jul 2009), with a potential rate of 0.42 and 1.75 GBS cases per million pandemic influenza vaccinations for age < 25 years and ≥ 25 years, respectively (Vellozzi, 2010). The event is considered potentially serious and severe, as it has a significant impact on patient's quality of life and/or may result in death, hospitalisation, persistent or significant disability/incapacity. Overall, GBS is generally associated with eventual favourable outcome, with most patients experiencing clinical improvement over weeks to months (Sejvar, 2011).

	<p>In infants and children, recovery is more rapid and tends to be complete, with fatalities being rare. Elderly patients have a worse prognosis. Overall, approximately 5-15% of patients die, and continued disability after 1 year has been estimated to be 20% of patients. Complete recovery is common in the remainder, although persistent mild weakness, numbness, pain and fatigue may be reported (Sejvar, 2011). GBS requires medical treatment (e.g. plasmapheresis, immunoglobulin), generally in a hospital setting (Sejvar, 2011).</p> <p>On the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, GBS is considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and is therefore classified as an important potential risk.</p>
Risk factors and risk groups	Incidence is higher in males, and increases with age. The risk period is considered to be the 6 weeks following immunization.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p><i>Guillain-Barré syndrome is described in Section 4.8 Undesirable effects of the Prepandemic vaccine, Focliva and Aflunov labels (SPC); and Section 4 of the Package Leaflet.</i></p> <p><u>Additional risk minimisation measures:</u></p> <p><i>No additional measures</i></p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p><i>PASS</i></p>

Important potential risk: Demyelination	
Evidence for linking the risk to the medicine	<p>The strength of evidence is low, as there have been no observed cases from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, inflammatory demyelinating disorders of the CNS are considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009), and have been reported vary rarely in association with influenza vaccine, with a potential rate of 0.03 multiple sclerosis cases, 0.064 of transverse myelitis, 0.04 for optic neuritis per million influenza vaccinations (Vellozzi, 2009).. The event is considered potentially serious and severe as it can have a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity. Demyelinating disorders require medical treatment (e.g. steroids/immunosuppressants) (Wingerchuk, 2005).</p> <p>On the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event, demyelinating disorders are considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and are therefore classified as an important potential risk.</p>
Risk factors and risk groups	There is insufficient evidence of any patient, dose-related or additive/synergistic risk factors; or of a specific risk period, in relation to demyelinating disorders specifically attributed to influenza vaccine.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p><i>Nervous system/neurological disorders are described in Section 4.8 Undesirable effects of the Prepandemic vaccine, Focliva and Aflunov labels (SPC); and Section 4 of the Package Leaflet.</i></p> <p><u>Additional risk minimisation measures:</u></p> <p><i>No additional measures</i></p>
Additional pharmacovigilance	<p><u>Additional pharmacovigilance activities:</u></p> <p><i>PASS</i></p>

activities	
Important potential risk: Bell's palsy	
Evidence for linking the risk to the medicine	<p>The strength of evidence is low, as a limited number of cases of Bell's palsy were observed from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, Bell's palsy is considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009), and have been reported vary rarely in association with influenza vaccines, with a potential rate of 0.29 Bell's palsy cases per million influenza vaccinations (Vellozzi, 2009). The event is considered potentially serious and severe as it may impact on patient's quality of life and/or may result in persistent or significant disability/incapacity Bell's palsy resolves spontaneously without treatment in most patients within 6 months (Wijnans, 2017).</p> <p>.On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, Bell's palsy is considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and is therefore classified as an important potential risk.</p>
Risk factors and risk groups	Risk factors include diabetes, weakened immune system and pregnancy. Risk period is generally considered to be 6 weeks.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p><i>Nervous system/neurological disorders are described in Section 4.8 Undesirable effects of the Prepandemic vaccine, Focliva and Aflunov labels (SPC); and Section 4 of the Package Leaflet.</i></p> <p><u>Additional risk minimisation measures:</u></p> <p><i>No additional measures</i></p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p><i>PASS</i></p>

Important potential risk: Immune thrombocytopenia	
Evidence for linking the risk to the medicine	<p>The strength of evidence is low, as a limited number of cases were observed from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, immune thrombocytopenia is considered a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), with one publication identifying 22 ITP events from 3.1 million influenza vaccinations (Liu, 2014). The event is considered potentially serious and severe as depending on the platelet count and clinical manifestations, the event may have a significant impact on patient's quality of life and/or may result in hospitalisation. Children typically recover spontaneously, in several weeks to months. In adults, spontaneous remission may occur, but it is uncommon after the first year of disease. Most post-immunisation episodes resolve within 3 months, although low platelet counts may rarely persist for more than 6 months (Wise, 2007). However, many patients have mild and stable disease with minimal or no bleeding. Life-threatening bleeding and death are rare (Kuter, 2017). Immune thrombocytopenia generally requires medical treatment (e.g. steroids/immunosuppressants, immunoglobulin, thrombopoietin receptor agonists) (Kuter, 2017).</p> <p>On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, immune thrombocytopenia is considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and is therefore classified as an important potential risk.</p>

Risk factors and risk groups	The risk period is considered to be 6 weeks after vaccination. There is no evidence of any patient, dose-related or additive/synergistic risk factors, in relation to immune thrombocytopenia specifically attributed to influenza vaccine.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>Thrombocytopenia is described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the Prepandemic vaccine, Foclivia and Aflunov labels (SPC); and Section 2 & 4 of the Package Leaflet.</i> <u>Additional risk minimisation measures:</u> <i>No additional measures</i>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <i>PASS</i>

Important potential risk: Vaccination failure	
Evidence for linking the risk to the medicine	The strength of evidence is low, as a limited number of cases of vaccination failure were observed from post-marketing or clinical trials. However, on the basis of evidence from the scientific literature, vaccination failure is considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009), with estimated effectiveness of adjuvanted pandemic vaccines being 80% (95% CI 59-90%) (Lansbury, 2017). The event is considered potentially serious and severe as it has the potential to lead to influenza virus infection. Depending on the clinical manifestations of the infection and characteristics of the host, the event may have a significant impact on patient's quality of life and/or may result in hospitalisation, or death. On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, vaccination failure is considered to potentially impact the benefit-risk profile of aH5N1 influenza vaccine, and is therefore classified as an important potential risk.
Risk factors and risk groups	Risk factors include immunodeficiency, mature age (due to senescence of immune responsiveness), suboptimal health status, and immunosuppressive therapy. Antibodies to influenza vaccination develop after approximately 2 weeks, therefore the risk period for vaccination failure is > 2 weeks after vaccination.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>Vaccination failure is described in Section 4.4 Special warnings and precautions for use of the Prepandemic vaccine, Foclivia and Aflunov labels (SPC); and Section 1 of the Package Leaflet.</i> <u>Additional risk minimisation measures:</u> <i>No additional measures</i>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <i>PASS</i>

Missing information: Use in pregnancy and lactation	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>Pregnancy and lactation is described in Section 4.6 Fertility, pregnancy and lactation of the Prepandemic vaccine, Foclivia and Aflunov labels (SPC); and Section 2 of the Package Leaflet.</i> <u>Additional risk minimisation measures:</u> <i>No additional measures</i>

Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> V87_27OB PASS
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Missing information: Use in children	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>Children are described in Section 4.2 Posology and method of administration, Section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties of the Prepandemic vaccine, Foclivia and Aflunov labels (SPC); and Section 3 & 4 of the Package Leaflet (excluding Foclivia)</i> <u>Additional risk minimisation measures:</u> <i>No additional measures</i>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> V87_30 PASS

II.C Post-authorisation development plan

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

As a specific obligation in the context of a marketing authorisation under exceptional circumstances (category 2), a PASS is planned in the situation of a pandemic, to confirm the safety profile of aH5N1c influenza vaccine. An update of the RMP with further details on additional pharmacovigilance activities will be submitted to competent authorities once a pandemic is declared.

There are no safety studies imposed as condition of the marketing authorisation (category 1), or required by the competent authority (category 3).

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

In the situation of a pandemic, for the missing information *Use in pregnancy and lactation*, the following study is planned:

- V87_27OB is a post-marketing, observational cohort study to evaluate the safety of aH5N1 (Foclivia[®]) in pregnant women (pregnancy registry). This study is planned for Great Britain in case of pandemic, and will follow from enrolment to pregnancy outcome and in live-born infants until 3 months of age.

As part of the Paediatric Investigation Plan (PIP), for the missing information *Use in children*, the following trial is planned:

- V87_30 (replaces V87_14) is a phase II, randomized, observer-blind, multicenter study to describe the immunogenicity and safety of several regimens altering the antigen and MF59 adjuvant content in a monovalent pandemic influenza vaccine (aH5N1) in healthy paediatric subjects aged 6 months to < 18 years. This protocol has been reviewed by competent authorities following submission, however is currently under amendment.