Summary of Risk Management Plan (RMP)

Flucelvax Tetra

(Quadrivalent Influenza Vaccine – cell-based (QIVc))

Suspension for injection in pre-filled syringe

Influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, of the types A / H1N1, A / H3N2, B / Yamagata and B / Victoria

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Based on Seqirus RMP version 2.0

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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 Flucelvax Tetra 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 Flucelvax Tetra in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Medius AG, Muttenz is fully responsible for the accuracy and correctness of the content of the published summary RMP of Flucelvax Tetra.

Part VI: Summary of the risk management plan

Summary of risk management plan for QIVc

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

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

It 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 QIVc's RMP.

I. The medicine and what it is used for

Flucelvax is authorised for prophylaxis of influenza for adults and children of 4 years of age and older. It contains Quadrivalent Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) as the active substance and it is a suspension for injection in pre-filled syringe. It is given by intra-muscular injection.

Further information about the evaluation of QIV's benefits can be found in QIVc's EPAR, including its plain-language summary, available on the EMA website, under the medicine's webpage (this to be edited by EMA)

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

II.A List of important risks and missing information

Important risks of QIVc together with measures to minimise such risks and the proposed studies for learning more about QIVc'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 packageleaflet 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 themedicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with orwithout prescription) can help to minimise its risks.

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

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

Important identified risks	None
Important potential risks	Neuritis
	Convulsion
	Encephalitis (ADEM)
	Vasculitis
	Guillain-Barré Syndrome
	Demyelination
	Bell's palsy
	Immune thrombocytopenia
Important missing information	Safety in immunocompromised patients
	Safety in subjects with underlying diseases
	Use in pregnant/breastfeeding women

II.B Summary of important risks

Important potential risk Neuritis	
Evidence for linking the risk to the medicine	Among many different types of neuritis the most frequently reported/described in the literature after vaccination are discussed below. Brachial plexus neuritis is a benign, self-limiting illness. The etiology is unknown; however, several factors have been implicated in triggering its onset such as trauma, infection, viral diseases, heavy exercise, surgery, immunization, and autoimmune mechanisms. Lumbosacral plexus neuritis is the lumbosacral counterpart of brachial plexus neuritis. The epidemiologic evidence to date is insufficient to assess an association between influenza vaccine and brachial neuritis. Publications reporting brachial neuritis after administration of an influenza vaccine did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence.
Risk factors and risk groups	Most cases of brachial neuritis occur in in persons between the ages of 20 and 60 years, although it has been reported in all ages. The incidence in males is

	two-to-four times greater than that observed in

	females (Shaikh, 2012).

Risk minimisation measures	None
Important potential risk Convulsion	
Evidence for linking the risk to the medicine	Reviews of different studies demonstrate a null association between influenza vaccine and seizures. In addition the publications did not provide evidence beyond temporality.
Risk factors and risk groups	Acute symptomatic seizures predominate in men, in the youngest age class, and in the elderly. Single unprovoked seizures predominate in men and in patients less than 12 months and older than 65 years (Hauser et al, 2008). Most febrile seizures occur in children between the ages of 6 months and 5 years. The peak age is 14–18 months, which overlaps with the ages when first doses of the MMRV, MMR, and varicella vaccines are recommended. A child who has already had a febrile seizure is more likely to have another one. Also if a member of a child's immediate family (a brother, sister, or parent) has had febrile seizures, that child is more likely to have a febrile seizure.
Risk minimisation measures	None
Important potential risk Encephalitis	
Evidence for linking the risk to the medicine	Review epidemiological studies was unable to draw definitive conclusions regarding an association between influenza vaccine and encephalitis/ encephalopathy. Viral infection and viral reactivation may contribute to the symptoms of encephalopathy; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.
Risk factors and risk groups	Although ADEM can occur at any age, it is more common in children (0.4 cases/100,000) (Huynh et al., 2008). For most vaccines, incidence rates are as low as 0.1 to 0.2 per 100,000 vaccinated individuals. ADEM following immunisation seems to occur significantly more frequently after primary vaccination as compared to revaccination. Postvaccination encephalomyelitis accounts for less than 5% of present cases of ADEM.
Risk minimisation measures	None

(Surface Antigen, Inactivated)

Potential risk Vasculitis	
Evidence for linking the risk to the medicine	A review of 48 publications reporting or studying onset or exacerbation of vasculitis after administration of an influenza vaccine. did not provide evidence sufficient evidence to conclude the vaccine may be a contributing cause of vasculitis. The symptoms described in the publications were consistent with those leading to a diagnosis of vasculitis, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Autoantibodies, T cells, complement activation, and immune complexes may contribute to the symptoms of vasculitis; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.
Risk factors and risk groups	Risk groups or risk factors vary depending on the type of vasculitis. In general, patients with underlying autoimmune disease such as rheumatoid arthritis or systemic lupus erythematosus, may be at increased risk of vasculitis.
Risk minimisation measures	None
Important Potential Risk Guillain-Barré Syndrome (GBS)	
Evidence for linking the risk to the medicine	Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis worldwide, and is thought to be immune-mediated. It is preceded by upper respiratory or gastrointestinal infection in about two-thirds of cases and is associated with some viral infections, including influenza. GBS has also been associated with the 1976 swine-influenza vaccine. Thereafter, some studies have shown a small increased risk of GBS following receipt of seasonal and 2009 H1N1 monovalent influenza vaccines. Studies over the years have also shown an increased risk of GBS following influenza infection, and the magnitude of risk is several times greater than that following influenza vaccination. Because GBS is rare, and even rarer following vaccination, it is difficult to estimate precise risk. Available studies are potentially limited by confounding by seasonality and by the association between influenza itself and GBS, which could mask an association between vaccine and GBS. In addition, strains of influenza targeted by the vaccine vary each year and associations with GBS also may vary.

	(Vellozzi C, Iqbal S, Broder K: Clinical Infectious Diseases, Volume 58, Issue 8, 15 April 2014, Pages 1149–1155)
Risk factors and risk groups	In the majority of studies that included incidence rates broken down by age, increases in rates were observed in most studies of people aged 50 years or more, with some showing a decrease in the highest age group of 60-80 years.
Risk minimisation measures	None
Important Potential Risk Demyelination	
Evidence for linking the risk to the medicine	Demyelination includes a varieties of diseases including ADEM and GBS that have been discussed above.
Risk factors and risk groups	Caucasian race is a risk factor. The incidence may be twice as high in Caucasians as in other races for which incidences are known. MS essentially is unknown among Eskimos and Bantus, and it is rare among Native Americans and Asians. MS is 5 times more prevalent in temperate climates than in the tropics, but the risk seems to be associated entirely with childhood years spent in a temperate climate. Throughout adulthood, the female-to-male ratio is 2:1. The sex ratio is more pronounced in those younger than 16 years (ie, approaches 3:1), but it is less pronounced in those older than the fifth decade. MS rarely occurs in those younger than 20 years or those older than 50 years. The occurrence of MS is even more rare in those younger than 15 years and in those older than 60 years.
Risk minimisation measures	None
Important Potential Risk Bell's Palsy	
Evidence for linking the risk to the medicine	Different available studies have been reviewed and none of these studies (Greene et al., 2010; Stowe et al., 2006) found a significantly increased risk of Bell's palsy after influenza vaccination. A review of the literature for mechanistic plausibility did not find any association beyond temporal relationship.

Risk factors and risk groups	The incidence of Bell's palsy increases between the ages of 10 and 30 years. Bell's palsy is least common in persons younger than 10 years and most common in those older than 70 years. Bell's palsy occurs more commonly in patients with diabetes and
	in pregnant women. No difference exists in sex distribution. In women, the overall incidence of Bell's palsy during pregnancy is comparable to that of all women of childbearing age; however, the incidence is high in the third trimester and correspondingly low during early pregnancy (Gilden et al 2004). Patients who have had one episode of Bell's palsy have an 8 percent risk of recurrence. Rarely, bilateral simultaneous Bell's palsy can occur at a rate of less than 1% of unilateral facial nerve palsy. Patients with underlying herpes virus may be at increased risk for Bell's palsy (Tiemstra and Khatkhate, 2007).
Risk minimisation measures	None
Important Potential Risk Immune thrombocytopenia	
Evidence for linking the risk to the medicine	Thrombocytopenia in childhood typically follows a viral illness. However, a transient but sometimes profound fall in platelet counts has also been reported after immunization against influenza. Prospective clinical trials measuring platelet counts before and after immunization with influenza did not demonstrate significant decreases of platelet counts. The Berlin Case-Control Surveillance Study, showed 3 cases of ITP in a review of 169 cases identified over 9 years.
Risk factors and risk groups	ITP is common in children, usually follows recovery from a viral illness or upper respiratory illness. Transient immunologic thrombocytopenia also complicates some cases of infectious mononucleosis, acute toxoplasmosis, or cytomegalovirus infections, and can be part of the prodromal phase of HIV or viral hepatitis. ITP has been reported in associations with several licensed vaccines including varicella vaccine, oral polio, and the MMR, but the largest number or reports, and those with the strongest evidence for causality, are in the case of the hepatitis B and influenza vaccines (Schattner, 2005).

Risk minimisation measures	None

Important missing/limited information	Safety in immunocompromised patients
Risk Minimization Measures	Routine activities. No additional risk minimization measures are considered necessary
Important missing/limited information	Safety in subjects with underlying diseases
Risk Minimization Measures	Routine activities. No additional risk minimization measures are considered necessary
Important missing/limited information.	Use in pregnant/breastfeeding women
Risk Minimization Measures	Routine activities. No additional risk minimization measures are considered necessary