Fluenz Tetra®

0.2 ml, Nasal spray, suspension in a single-use nasal applicator

Summary of the Risk Management Plan (RMP) for Fluenz Tetra® Reassortant influenza virus strains (live attenuated) of types A/H1N1, A/H3N2, B/Yamagata and B/Victoria

Document Version: 1.0

Document Date: 12-May-2022
Based on EU RMP version 10, 05-May-2021, Data lock point 31 Aug 2020

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 Fluenz Tetra® is a concise document and does not claim to be exhaustive.

As the RMP is an european 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 Fluenz Tetra® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "AstraZeneca AG" is fully responsible for the accuracy and correctness of the content of the published summary RMP of Fluenz Tetra®.

VI: 1 THE MEDICINE AND WHAT IT IS USED FOR

FLUENZ TETRA is authorised for Prophylaxis of influenza in children from 24 months to less than 18 years of age. It contains Influenza vaccine (live attenuated, nasal) as the active substance and it is given by nasal route of administration, one 0.2-mL dose (administered as 0.1 mL per nostril).

VI: 2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Fluenz Tetra, together with measures to minimise such risks and the proposed studies for learning more about Fluenz Tetra'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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine *pharmacovigilance activities*.

VI: 2.1 LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Fluenz Tetra 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 Fluenz Tetra. 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.

Table 0-1 List of important risks and missing information

Important identified risks	None
Important potential risks	Guillain-Barré syndrome Influenza-like illness due to inadvertent administration or secondary transmission to severely immunocompromised patients Seizures and convulsions Vaccination failure (Lack of efficacy) Narcolepsy with or without cataplexy
Missing information	None

VI: 2.2 Summary of important risks

Table 0-2 Important potential risk – Guillain-Barré Syndrome

Evidence for linking the risk to the medicine	The 1976 swine flu vaccine (inactivated) in the US was associated with an increased risk of GBS. Following the 2009 pandemic a study of pooled data from 23 million persons vaccinated within the US federal systems found an attributable risk of 1-3 additional GBS cases per million persons vaccinated. Evidence for causal association of GBS with other influenza vaccines is inconclusive. No events of GBS were reported in the clinical trial programme and isolated reports have been received from post-marketing experience.
Risk factors and risk groups	GBS is more common in male patients and older adults (risk increases with age, and people older than 50 years are at greatest risk for developing GBS). GBS is generally associated with respiratory or gastrointestinal infection (in approximately 70% of cases), infection with *Campylobacter jejuni*, *cytomegalovirus* and or *Epstein Barr virus*, surgical procedures, malignancy, pregnancy, autoimmune diseases, and drug exposure (captopril, danazol, zimeldine, amitriptyline, and gangliosides). In addition to the general risk factors for GBS no further risk factors have been identified from the individual case safety reports received.

Table 0-2 Important potential risk – Guillain-Barré Syndrome

Risk minimisation measures	Routine risk minimisation measures: • SmPC section: ”Undesirable effects”
Additional pharmacovigilance activities	None

Table 0-3 Important potential risk – Influenza-like illness due to inadvertent administration or secondary transmission to severely immunocompromised patients

Evidence for linking the risk to the medicine	LAIV contains live attenuated influenza viruses that infect and replicate in cells lining the nasopharynx of the recipient to induce immunity. Vaccine viruses capable of replication can be cultured from nasal secretions obtained from vaccine recipients, although at much lower titres than contained in the vaccine. Although shedding of vaccine strains from individuals who have received LAIV rarely results in transmission of the vaccine virus to others, there are potential safety risks for unintended recipients who are severely immunocompromised, such as bone marrow transplant patients. An immunocompromised patient who receives the vaccine could experience symptoms of influenza or influenza-like illness, but the attenuated characteristics of the LAIV virus strains could lead to milder illness than wild-type influenza. There was no evidence of influenza-like illness in post-marketing studies in children with immunosuppression and there have been isolated case reports from the post-marketing experience.
Risk factors and risk groups	Severely immunocompromised individuals, including bone marrow transplant recipients, and clinically immunocompromised patients with cancer, symptomatic HIV, or those receiving immunosuppressive drug therapy.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section:”Contraindications” and “Warnings and precautions”
Additional pharmacovigilance activities	None

Table 0-4 Important potential risk - Seizures and convulsions

Evidence for linking the risk to the medicine	Some studies have detected a small increased risk of febrile seizures in young children following the receipt of IIV in some flu seasons. In these studies, the risk of febrile seizures was increased for children 12 through 23 months of age, particularly when the inactivated vaccine was given at the same time as pneumococcal conjugate vaccine (PCV13) and diphtheria, tetanus, and pertussis (DTaP)-containing vaccine. Seasonal flu vaccines were not found to be associated with febrile seizures in children. There have been very rare reports of seizure reported during the post marketing experience.
Risk factors and risk groups	In the non-vaccinated population males and Blacks have higher incidence rates of convulsive disorders than females and Whites. Other risk factors for seizures are infections, toxic exposure, fever or metabolic abnormalities. The rate of recurrence of febrile seizures in children is approximately 33%. A predisposition exists as evidenced by an increased risk in families with positive history. There is increased risk of febrile seizures when flu vaccines are given at the same time as other vaccines. In addition to the general risk factors for seizures, risk factors from the spontaneous case reports included: preterm birth and developmental delay.
Risk minimisation measures	None
Additional pharmacovigilance activities	None

Table 0-5 Important potential risk - Vaccination Failure (Lack of effect)

Evidence for linking the risk to the medicine	Effectiveness of Q/LAIV against A/H1N1 strains, which were the most frequent circulating strains during the 2013-2014 and 2015-2016 US influenza season, was lower than expected and not statistically significant in a study conducted by the company (MA-VA-MEDI3250-1116): 13% (95% CI: 55 to 51%) for 2013-2014 and 50% (95% CI: -2, 75) for 2015-2016. There have been isolated reports of vaccination failure (lack of efficacy) in the post-marketing experience.
Risk factors and risk groups	Based on data currently available, it appears that the most likely cause of lower than expected effectiveness is the reduced replicative fitness of the post-pandemic H1N1 strains included in the vaccine. New virus characterization assays were incorporated into the strain selection process to select strains with improved replicative fitness.
Risk minimisation measures	No specific risk factors for decreased efficacy have been identified in clinical trials and post-marketing experience.
Additional pharmacovigilance activities	Studies: MA-VA-MEDI3250-1116. See section 0 of this summary for an overview of the post-authorisation development plan.

Table 0-6 Important potential risk - Narcolepsy with or without cataplexy

Evidence for linking the risk to the medicine	Studies in Finland, Sweden, Norway, England, and France have shown an increase in the relative risk of narcolepsy when patients were vaccinated with Pandemrix. More recent Vigibase data from 2009 through August 2015 show that the UK percentage of all N/C reports has risen from 1.2% to 29.9% over the last four years, consistent with publicity stimulation of reporting for purely coincidental cases or a general effect of influenza vaccine antigens or a combination of both factors. There have been isolated reports of N/C in the post-marketing experience.
Risk factors and risk groups	Individuals with the HLA- DBQ1*06:02 as do patients with family-history of narcolepsy, autoimmune disorders and brain injury have a higher likelihood of developing narcolepsy. Most cases occur after 6 years and before 40 years of age. Some studies have suggested the condition may be more common in men. No risk factor for N/C has emerged from review of post-marketing cases apart from their mostly pediatric ages (reflecting the European age indication). Only one spontaneous report provided the patient's HLA type (HLA DQB1-06:02).
Risk minimisation measures	None
Additional pharmacovigilance activities	None

VI: 2.3 Post-authorisation development plan

VI: 2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations for Fluenz Tetra.

Vi: 2.3.2 Other studies in post-authorisation development plan

MA-VA-MEDI3250-1116: A Case Control Study of the Effectiveness of Q/LAIV Versus Inactivated Influenza Vaccine and No Vaccine in Subjects 2-17 Years of Age.

Purpose of the study: The objective of this study is to evaluate the effectiveness of a Q/LAIV compared to inactivated influenza vaccine (IIV) or no vaccine in community-dwelling subjects 2 through 17 years of age against laboratory-confirmed influenza.