VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

The influenza (flu) virus typically causes symptoms like runny nose, cough, high fever, headache, achiness, and sense of feeling very ill. However it can develop into more serious conditions such as pneumonia (lung infection) or inflammation in other organs like the heart and brain, and cause death. Those at highest risk of developing complications are young children the elderly, pregnant women, and anyone with chronic conditions such as asthma or heart disease.

The flu usually occurs in the winter months and can be caused by different types (strains) of the virus from year to year. The World Health Organization (WHO) tries to predict which strains of flu are most likely to infect people each year and these are included in the flu shot for that year.

One of the best ways to prevent the flu is by getting a flu vaccine at the start of flu season each year.

VI.2.2 Summary of treatment benefits

Populations 3 years and older

Study **FLU D-QIV-003** examined whether FLU D-QIV was as effective as another (trivalent) influenza vaccine in over 4000 people from 3 to 17 years who received either vaccine. The immune response against influenza A or B strains in children after either vaccine was tested and FLU D-QIV was found to be as effective as the trivalent influenza vaccination. It was also shown to be safe.

Study **FLU D-QIV-008** compared the immune response and safety of FLU D-QIV to trivalent influenza vaccines in people 18 years of age or older. Around 4600 people received either FLU D-QIV or trivalent influenza vaccine. FLU D-QIV was shown to be as good as the trivalent vaccines in producing immune responses against viral strains that were in both vaccines and also showed better immune responses against vaccine strains that weren't in trivalent vaccines.

Children 6 to 35 months of age

Study **FLU D-QIV-004** compared how well FLU D-QIV prevented influenza A and/or B disease to non-influenza vaccines. Over 12,000 children participated in this study. FLU-QIV was shown to be safe and effective in preventing influenza A and/or B disease of any severity and also shown to be effective in preventing moderate to severe influenza A and/or B disease.

VI.2.3 Unknowns relating to treatment benefits

Not Applicable.

VI.2.4 Summary of safety concerns

Important identified risks

There have been no important identified risks found with the usage of FLU D-QIV during the clinical development program.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Anaphylaxis (Life-threatening allergic reaction)	Life-threatening allergic reactions have been reported in people who had flu shot. People allergic to any ingredients in FLU D-QIV vaccine could have an allergic reaction to flu shot. The viruses for the flu shot are grown in eggs; therefore, people allergic to eggs could have an allergic reaction to FLU D-QIV. The majority of reactions probably are caused by residual egg protein in the vaccine [CDC, 2010].
Fits when having fever (febrile convulsion)	In April 2010, there was a reported increase in febrile seizures following influenza vaccination in young children in Western Australia. Following extensive investigations into this safety issue, epidemiological analyses determined that administration of the 2010 seasonal influenza vaccines, Fluvax® and Fluvax Junior® (manufactured by Bio CSL), was associated with an increased risk of febrile convulsions. The rate of febrile convulsions was found to be up to 1 per 100 (1%) children under age 5 years vaccinated with this vaccine [TGA, 2010], but the risk has not been confirmed for other influenza vaccines, including FLU D-QIV.
Inability to move one side of the face (Bell's palsy)	Bell's palsy has been reported in people who had influenza vaccine within the nose. Researchers have not found a link between Bell's palsy and influenza vaccines that are given by injection.
Paralysis that starts in the feet and moves up (Guillain-Barré syndrome or GBS)	GBS has been reported to occur in approximately 1 or 2 people out of every million people who receive seasonal influenza shot.
Injection site bleeding in patients with blood clotting illness (Injection site hemorrhage in individuals with thrombocytopenia or any coagulation disorder)	Bleeding may occur at the injection site in populations at increased risk of hemorrhage, such as those with thrombocytopenia or acquired/hereditary coagulation disorders.
Administration error due to mix- up of vaccine brands	Administration errors due to mix-up of two vaccine brands may occur when two vaccines with similar brand names are co-marketed in the same country.
Excessive daytime sleepiness and sudden attacks of sleep (Narcolepsy)	Early laboratory results suggest a homologous sequence between hypocretin, the protein that controls the sleep-wake cycle, and a protein on the surface of the H1N1 influenza virus, in samples from unvaccinated narcoleptic patients. However, to date, there is no clinical evidence suggesting that the H1N1 viral protein used in seasonal influenza shot increases the risk of narcolepsy. Even though further research is needed to understand whether exposure to H1N1 viral protein in wild virus or seasonal

Risk	What is known (Including reason why it is considered a potential risk)
	flu shots may be linked with an increased risk of narcolepsy, GSK has decided to include narcolepsy as a potential risk in Risk Management Plans for GSK H1N1-containing seasonal influenza vaccines, including FLU D-QIV, as a precautionary measure.

Missing information

Risk	What is known
Use during pregnancy and lactation	The safety of FLU D-QIV when administered to pregnant or breast-feeding women has not been evaluated.

VI.2.5 Summary of additional risk minimisation measures by safety concern

The Summary of Product Characteristics and the Package leaflet for FLU D-QIV can be found in the FLU D-QIV EPAR page. This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
FLU D-QIV-004	To demonstrate the efficacy of FLU D-QIV vaccine compared to non-influenza vaccine controls in the prevention of RT-PCR confirmed moderate to severe influenza A and/or B disease and of RT-PCR confirmed influenza A and/or B disease of any severity in children aged 6 to 35 months. The immunogenicity, reactogenicity and	To demonstrate the efficacy, reactogenicity and safety of FLU D-QIV in children 6 to 35 months in order to ask for an extension of the current indication in children 6 to 35 months.	Completed	Q3 of 2017 in EU

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	safety of FLU D-QIV will also be assessed.			
FLU D-QIV-009 EXT-004	To evaluate the priming effect of FLU D-QIV by assessing the immune response after 1 dose of FLU D-QIV in primed children compared to unprimed children	To assess the priming effect of FLU D-QIV	Completed	Q3 of 2017 in EU
Flu-DQIV-010	To evaluate the immunogenicity and the safety of FLU D-QIV when co-administered with the pneumococcal polysaccharide vaccine (PPV23) in adults ≥ 50 years who are at higher risk of developing IPD (invasive pneumococcal disease) and complications from influenza infection.	To assess the immunogenicity and safety of the co-administration of FLU D-QIV with PPV23 in adults with underlying medical conditions	Completed	Q3 of 2017 in EU
EPI-FLU-019 VE CA	To evaluate the effectiveness of *FluLaval* in the prevention influenza associated hospitalization in older adults ≥ 65 years of age and in persons 16- 64 years of age, respectively		Completed	June 2016 (Year 1, 2, and 3 reports). Submitted in EU March 2017 (Year 4 report). Planned submission on Q3 of 2017 in EU
Zoster-004	To assess the immunogenicity, reactogenicity and safety of FLU D-QIV when co-administered with the GSK Biologicals Herpes Zoster Candidate vaccine in adults aged ≥ 50	To assess the immunogenicity and safety of the co-administration of FLU D-QIV with Zoster Vaccine in adults ≥ 50 years	Completed	March 2016

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	years compared to the administration of the vaccines separately			
EPI-FLU-045 VS UK	Influenza vaccine safety surveillance in the UK (pilot)		Completed	March 2016
EPI-FLU-046 VS UK	Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England		Completed	July 2017
EPI-FLU-050	A prospective, observational, multi-center, drug use investigation to monitor the safety of GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, *Fluarix* Tetra when administered according to the approved Prescribing Information in Korea.		Ongoing	December 2021
EPI-FLU-055	Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Pilot study in England 2017/18		Planned	June 2018

Studies which are a condition of the marketing authorisation

None of the above studies is a condition of the marketing authorisation.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	September 2012	Anaphylaxis added as a potential risk Haemorrhage in individuals with thrombocytopenia or any coagulation disorder added as a potential risk	Language on these two new potential risks was added into section 3 (Evaluation of the Need for Risk Minimisation Activities) and section 5 (Summary of the Risk Management Plan)
3.0	January 2013	Administration error due to mix-up of vaccine brands was added as a potential risk	A plan was established to ensure brand traceability and to actively monitor such potential errors
4.0	May 2013	The RMP was updated to its new format in compliance with New Pharmacovigilance Legislation and in preparation for future registration in additional EU countries	
5.0	August 2013	Section SIV.4 (Conclusions on the populations not-studied and other limitations of the clinical trial development programme) was amended per request from PEI	Amendment done as a follow up to variation DE/H/1939/1/IB/005
6.0	April 2014	Limited data available in subjects less than 3 years of age was added to the "Missing Information" section, per request of the	Per same request from Belgium Regulatory Authority, the word "Important" was

Version	Date	Safety Concerns	Comment
		Belgium Regulatory Authority The recommendation not to use FLU D-QIV in subjects less than 3 years of age was also included as a Risk Minimization Effort, per Belgium Regulatory Authority request In response to the Interim Guidance on Enhanced Safety Surveillance for Seasonal Influenza Vaccines in the EU (EMA/PRAC/135943/2014), a statement was added on GSK commitment to submit a proposal for enhanced safety surveillance with a future update of the RMP, and to perform enhanced safety surveillance for FLU D-QIV GSK added narcolepsy as a potential risk to the Risk Management Plan based on data from a research laboratory in the US which suggests that vaccination with H1N1-containing vaccines might lead to an immune response that potentially could trigger the development of narcolepsy.	removed from the phrase “Important Missing Information” Although there is no clinical evidence as of the date of this Risk Management plan showing that such an immune response is triggered, GSK, as a precautionary measure, has decided to include narcolepsy as a potential risk.
7.0	August 2014	A high level description on the type of the planned enhanced safety surveillance was included	

Version	Date	Safety Concerns	Comment
		along with timelines for the planned start of this activity, as requested by the PEI	
8.0	May 2015	Information regarding study EPI-FLU-045 VS UK was added to the Risk Management Plan per request from the PEI	
8.1	October 2015	The Risk Management Plan was updated to correct the section of the plan in which Study EPI-FLU-045 VS UK was mentioned. It had been mistakenly mentioned in the section III.4.2 of the RMP in version 8.0, instead of section III.4.3	
9.0	June 2016	As requested by the PEI, the plan was updated with commitments for Enhanced Safety Surveillance, consisting of the EPI-FLU-045 VS UK study (for 2015-2016 season) and EPI-FLU-046 VS UK study (for 2016-2017 season), and status of the EPI-FLU-019 VE CA effectiveness study	
10.0	February 2017	The Risk Management Plan was updated to include safety, efficacy and immunogenicity data from clinical study FLU D-QIV-004 in children 6 to 35 months of age in preparation for a proposed indication of FLU D-QIV in this age group	

Version	Date	Safety Concerns	Comment
11.0	July 2017	The Risk Management Plan was updated with status for Enhanced Safety Surveillance, consisting of the EPI-FLU-046 VS UK, EPI-FLU-055 VS UK; the EPI-FLU-019 VE CA effectiveness study, the FLU-D-QIV-010 co-administration study as well as update related to IMI DRIVE Vaccine Effectiveness EU project	