13.3 Part VI.2 Elements for a Public Summary

13.3.1 Part VI.2.1 Overview of disease epidemiology

Influenza is a highly contagious respiratory disease that can cause can cause epidemics. It can cause people to feel severely unwell and sometimes cause death, either through influenza illness itself or pneumonia (chest infection) or by making a medical conditions worse, (e.g. if the patient has heart disease or chronic chest disease). Although the risk of complications is higher in elderly patients or people that already have medical illnesses, the influenza virus can cause severe illness or death in young people and people who were previously healthy.

On average, it is estimated that each year between 5 to 10 out of every hundred adults who come into contact with the influenza virus will become infected and about 20 to 30 children out of every hundred exposed to the virus will become infected. It tends to infect people very quickly: symptoms can start 1-4 days after being exposed to the virus.

13.3.2 Part VI.2.2 Summary of treatment benefits

Vaccines can offer some protection from infection by influenza virus. Vaccination may reduce the number of hospitalizations by up to a third and has also been shown to reduce overall number of deaths from influenza-related illness by up to two thirds during influenza seasons.

13.3.2.1 Current (gold) standards of treatment

Influenza vaccination is the primary method for preventing influenza and its severe complications.

Each year, the virus mutates and a new strain emerges. Because many people will never have been exposed to the new strain of virus, they do not have any resistance and an epidemic

could occur. The influenza vaccine is therefore updated each year to make sure it is well matched to new influenza virus strains that are expected to cause epidemics.

Antiviral drugs are sometimes used in the treatment of influenza; however, these agents are not a substitute for vaccination. There are four currently licensed antiviral agents against influenza in the US: amantadine, rimantadine, zanamivir, and oseltamivir. Some new influenza viruses are resistant to amantadine and rimantadine; therefore, these drugs are not recommended in the US.

13.3.2.2 Where the medicinal product fits in the therapeutic armamentarium (i.e. 1st line, relapse, etc.)

Agrippal is a vaccine to prevent influenza, especially in those who run an increased risk of associated complications. Influenza vaccine should be used in accordance with Official Guidance.

When a person is given the vaccine, the immune system (the body's natural defense system) will produce its own protection (antibodies) against the disease. None of the ingredients in the vaccine can cause flu.

13.3.2.3 A brief statement of the standard against which the medicine was judged: number of patients in pivotal studies and treatment regimes

Agrippal is a vaccine that will help protect against influenza (flu), particularly in subjects who run a high risk of associated complications. Agrippal has shown to be safe and immunogenic. A total of 25,412 subjects have received Agrippal prophylaxis in company-sponsored investigational clinical trials and there is extensive-post-marketing data.

13.3.2.4 Results in lay language

Agrippal was found to have an acceptable safety profile during the clinical trials. These trials showed that Agrippal vaccine can help the body produce antibodies against the influenza viruses (A/H3N2, A/H1N1, and B). The trials also found that Agrippal can be administered at the same time as other licensed vaccines in healthy subjects.

13.3.2.5 Post-authorization data which impacts on efficacy

The LIVE study, C70P1OB, (comparative effectiveness and safety of Fluad vs Agrippal in Italy) showed that vaccination with Fluad reduced the risk of hospitalization for influenza or pneumonia in the elderly during the peak of the influenza season by 25% relative to vaccination with Agrippal.

13.3.3 Part VI.2.3 Unknowns relating to treatment benefits

Not applicable.

13.3.4 Part VI.2.4 Summary of safety concerns

Table 13-4 Important identified risks

Risk	What is known

Risk	What is known
Anaphylactic reactions	Some patients can develop allergic reactions following vaccination, possibly with shortness of breath, wheezing, swelling of the throat, or leading to a dangerous decrease of blood pressure, which, if untreated, may lead to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

Table 13-5 Important potential risks

Risk	What is known
Neuritis (inflammation of nerves)	There have been a s mall number of reports of inflamed nerves following influenza vaccination. This event can occur in people who have not received any vaccination.
Convulsions (fits)	Convulsion following vaccination is rare. It can occur with or without fever. Febrile convulsions (fits associated with high fever) are more common in children. There is a greater risk of convulsions in people who have epilepsy.
Encephalitis (inflammation of the central nervous system)	There have been very rare reports (less than 1 in 10,000 people) of symptoms of encephalitis following influenza vaccinations. This event can occur in people who have not received any vaccination.
Vasculitis (inflammation of the blood vessels which can cause skin rashes, joint pain, and kidney problems)	There have been very rare reports (less than 1 in 10,000 people) of inflammation of blood vessels following influenza vaccinations. This event can occur in people who have not received any vaccination.
Guillain-Barré syndrome (a type of paralysis)	There have been very rare reports (less than 1 in 10,000 people) of a type of paralysis called Guillain-Barré syndrome following influenza vaccinations. This event can occur in people who have not received any vaccination.
Demyelination (a disorder of nerves such as multiple sclerosis)	There have been some reports of symptoms that may be due to demyelination (including pains or loss of sensation or function along any particular nerve in the body). This event can occur in people who have not received any vaccination and the causes are not fully understood.
Bell's palsy (paralysis of the facial nerve leading to drooping of one side of the face)	There have been some reports of paralysis of the facial nerve leading to drooping of one side of the face following influenza vaccinations, in particular with vaccines that can be administered through the nose. This event can occur in people who have not received any vaccination and the causes are not fully understood.
Thrombocytopenia	A low number of platelets, which are important in blood clotting and preventing bleeding.

Risk	What is known
Vaccination failure (developing influenza despite being vaccinated)	Not every person who is vaccinated against influenza will be fully protected. There are several reasons for this, including the emergence of new strains of the virus that are resistant to the vaccine, infection with other types of influenza, and sometimes people do not develop the immune response following vaccination for other reasons. Seqirus assesses every report of vaccination failure to ensure that there is no chance that the event was due to a problem with the vaccine itself. So far the vaccine is not considered to have led to any vaccination failure reports through any manufacturing defect or problem with quality. However, as influenza is a severe and sometimes life-threatening event, Seqirus closely monitors vaccination failure on a routine basis.

Table 13-6 Missing information

Safety in subjects with underlying diseases or immunocompromised patients	There is limited experience in this population. It is believed that patients with chronic severe underlying medical conditions and patients whose immune systems are not working properly may be less able to make sufficient antibodies following influenza vaccination. The available information in this population has not raised any specific safety concern.
Use in pregnant women	Flu vaccines can be used in all stages of pregnancy. Larger datasets on safety are available for the second and third trimester, compared with the first trimester; however, data from worldwide use of flu vaccines does not indicate that the vaccine would have harmful effects on the pregnancy or the baby. Seqirus advises patients to “Tell your doctor or pharmacist if you are pregnant or think you may be pregnant.”

13.4 Part VI.2.5 Summary of additional risk minimization measures by safety concern

No additional risk minimization measures are considered necessary for any of the safety concerns

13.5 Part VI.2.6 Planned post authorization development plan

13.5.1 List of studies in post authorization development plan

Table 13-7 List of studies in post authorization development plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
V71_22. A Multi-Centre Phase IV, Randomised, Controlled, Double-Blind Study to Evaluate	To collect safety and immunogenicity data in healthy adults aged 50	Safety of the vaccine in adults aged 50 and above	FSFV 01MAY2012	Final study report Q4 2014

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
the Immunogenicity, Safety, and Tolerability of a Trivalent Subunit Inactivated Influenza Vaccine in Health Subjects Aged 50 Years and Above.	years and above.			
V58P15 A Phase III, Observer-Blind, Randomised Multicenter Study to Evaluate of Trivalent Subunit Influenza Vaccines, Produced Either in Mammalian Cell Culture (TIVc) or in Embryonated Eggs (TIV), in Children and Adolescents of 3 to <18 Years of Age at High Risk for Influenza-Related Complications	To evaluate the Safety of Trivalent Subunit Influenza Vaccines, Produced Either in Mammalian Cell Culture (TIVc) or in Embryonated Eggs (TIV), in Children	Safety in Adolescents 3 to 17 Years of Age at Risk for Influenza-Related Complications in Healthy Children and Adolescents Aged 3 to 17 Years.	FSFV 22JUL2013	Final study report Q4 2014
V71_25OB Post-marketing Surveillance of Agriflu (the US licensed analog to Agrippal) Safety in Pregnancy (Pregnancy registry)	To investigate pregnancy outcomes after vaccination with Agrippal (name of vaccine is Agriflu in the US).	Major congenital malformations	Pending launch of Agrippal on US market.Draft protocol to be submitted to FDA prior to start of the registry.	To be defined upon launch of Agrippal on the US market

13.5.2 Studies which are a condition of the marketing authorization

There are no studies that are conditions of the marketing authorization.

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

Major changes to the Risk Management Plan over time

From RMP version 1 (dated 12 July 2010) until version 6.1 (current version dated September-2017), there have been some changes regarding safety concerns that are summarised in Table 13-8 below.

Table 13-8 Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	August 2011	Important dentified risks: N/A Important potential risks: convulsion	Event term “grand mal convulsion” added
3.0	May 2012	Identified risks:anaphylaxis Potential risks:thrombocytepenia	Moved from potential to identified risk Was added as potential risk
4.0	May 2013	Extensive limb swelling was added as new identified safety concern and Vaccination failure as new potential risk	
5.0 (current version)	June 2014	Safety in children and elderly Enhanced safety surveillance	Children and elderly groups will no l onger be considered “Missing Information”. Enhanced safety surveillance of seasonal influenza vaccines according to the new Interim guidance for in the EU (EMA/PRAC/222346/2014)
5.1		Enhanced safety surveillance	Enhanced passive safety surveillance of seasonal influenza vaccines according to the Interim guidance for in the EU (EMA/PRAC/222346/2014)
6.0	10 January 2017	NA	Enhanced passive safety surveillance of seasonal influenza vaccines according to the Interim guidance in the EU (EMA/PRAC/

			222346/2014). ELS has been removed as an important identified risk. Endorsed by PRAC (Procedure No.: PSUSA/00001744/201508)
6.1	September 2017	NA	Development of Robust Innovative Vaccine Effectiveness