VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Influenza is a very infectious illness which occurs in outbreaks during winter, in countries from both the Northern and Southern Hemispheres. It is spread by the air when people infected with influenza sneeze, cough, or speak. The most common types of influenza are called influenza A/H3N2, influenza A/H1N1 and influenza B.

People who are infected with influenza experience symptoms such as fever, muscle aches, headache, cough, sore throat, runny nose and generally feeling unwell (malaise). It can be difficult for healthcare professionals to distinguish an infection caused by influenza virus from an infection caused by other viruses. For this reason, laboratory testing is sometimes required to diagnose influenza. In general, people infected with influenza recover after 2 – 7 days, although it may take a longer time for other symptoms such as cough and malaise to resolve.

For some people, including older persons (aged older than 65 years of age), persons with long-term diseases (such as airway or heart diseases, diabetes, kidney diseases or immune system diseases) and young children (newborns to 2 years old), influenza infection can lead to serious complications and subsequent hospitalization. When pregnant women are infected with influenza, the likelihood of premature birth is increased and these women are more likely to be admitted to hospital and to have serious complications such as pneumonia.

Outbreaks of influenza are caused by one or more of the three common types of influenza virus (influenza A/H3N2, influenza A/H1N1 and influenza B). Influenza vaccines are designed to protect people who are vaccinated against illness from these three types of virus. They contain an inactivated (or killed virus) version of each of these three types of influenza.

These influenza vaccines, including CSL's influenza vaccine, have been used in many parts of the world for almost 50 years. Many different government health bodies worldwide recommend people get the influenza vaccine, especially older persons, people with long-term diseases, and young children.

The influenza vaccine is estimated to provide protection against influenza in approximately 70 – 90% of healthy people. The influenza vaccine is less protective against influenza in older persons, but still can reduce the severity of the infection and serious complications.

VI.2.2 Summary of treatment benefits

In terms of prevention of influenza infections, influenza vaccination is the only option available. CSL's influenza vaccine is an inactivated (or killed virus) vaccine, which is given by injection. CSL's influenza vaccine can be given to adults and children from 5 years of age.

CSL's influenza vaccine has been used in numerous clinical trials. Overall, 11,556 healthy adults (18 years to less than 65 years), 1,067 older adults (65 years and older) and 3,331 children (6 months to less than 18 years) were included. The results from these clinical trials showed that CSL's influenza vaccine was safe and effective for prevention of influenza infection in the patients included.

The safety and efficacy of influenza vaccines, including CSL's influenza vaccine, are also supported by approximately 50 years use in the market.

VI.2.3 Unknowns relating to treatment benefits

Though certain populations were not included in CSL's clinical trials, such as pregnant or breast feeding women, or people with long-term diseases (including airway or heart diseases, diabetes, kidney diseases or immune system diseases), different government health bodies worldwide recommend these people get the influenza vaccine, as they are considered to be at a higher risk of infection and potential complications from influenza.

A pregnancy study is ongoing, with the aim to obtain further information on the use and safety of CSL's influenza vaccine in pregnant women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Fever and seizures/convulsions ('fits') in young children	Children under 5 years of age can experience fever and seizures/convulsions ('fits') with CSL's influenza vaccine. Children aged between 5 years and 8 years	CSL's influenza vaccine should not be used in children under 5 years of age. For children aged 5 to less than 9 years old, healthcare professionals (e.g. General

Risk	What is known	Preventability
	can experience fever with CSL's influenza vaccine. Although these are considered serious reactions, most children recover after treatment.	Practitioners (GPs), nurses) should assess whether it is appropriate for the child to receive CSL's influenza vaccine
Severe allergic reaction (anaphylaxis)	Anaphylaxis is a severe allergic reaction which can occur with influenza vaccines. Symptoms can include difficulty breathing and severe swelling, which could lead to death. However, anaphylaxis is considered very rare, and most people recover after treatment.	Influenza vaccine should not be used in people who have experienced a severe allergic reaction to influenza vaccine in the past, or to any of the ingredients in the influenza vaccine

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Inflammation of the brain (encephalomyelitis)	Encephalomyelitis is a condition involving inflammation of parts of the central nervous system (includes the brain and spinal cord), which could potentially occur after receiving influenza vaccines. The condition is severe, with symptoms including confusion, loss of consciousness, seizures/convulsions or coma, which can lead to permanent disability or death. However, encephalomyelitis related to influenza vaccine is considered very rare, and there is not enough information to determine if this condition is definitely caused by influenza vaccines.
Seizures/convulsions ('fits')	Seizures/convulsions ('fits') are a condition which could potentially occur after receiving influenza vaccines. Seizures/convulsions involve body muscles contracting and relaxing rapidly and repeatedly, which results in an uncontrolled shaking of the body. The condition is considered relatively common in general; however, seizures/convulsions related to influenza vaccine are considered very rare. There is not enough information to determine if this condition is definitely caused by influenza vaccines.
Inflammation of the nerve	Guillain-Barré syndrome is a syndrome involving

Risk	What is known (Including reason why it is considered a potential risk)
system (Gullian-Barré syndrome)	inflammation of the 'peripheral' nervous system (the nerve system outside of the central nerve system [brain and spinal cord]), which could potentially occur after receiving influenza vaccines. The syndrome is severe, with symptoms including weakness/numbness of the limbs and paralysis, which can lead to hospitalisation. However, Guillain-Barré syndrome related to influenza vaccine is considered very rare, and there is not enough information to determine if this syndrome is definitely caused by influenza vaccines.
Inflammation of the nerves in the spinal cord (transverse myelitis)	Transverse myelitis is a condition involving inflammation of the spinal cord, which could potentially occur with influenza vaccines. The condition is severe, with symptoms including back pain and weakness/numbness of the limbs, which can lead to permanent disability. However, transverse myelitis related to influenza vaccine is considered very rare, and there is not enough information to determine if this condition is definitely caused by influenza vaccines.
Inflammation of the nerves in the eye (optic neuritis)	Optic neuritis is a condition involving inflammation of the nerves in the eye, which could potentially occur after receiving influenza vaccines. Symptoms can include eye pain and loss of vision on one side, which usually resolves by itself or with treatment. Optic neuritis related to influenza vaccine is considered very rare, and there is not enough information to determine if this condition is definitely caused by influenza vaccines.
Inflammation of the nerves in the face (Bell's palsy)	Bell's palsy is a condition involving inflammation of the nerves in the face, which could potentially occur after receiving influenza vaccines. Symptoms can include facial drooping on one side, which usually resolves by itself or with treatment. Bell's palsy related to influenza vaccine is considered very rare, and there is not enough information to determine if this condition is definitely caused by influenza vaccines.
Allergic reaction (serum sickness)	Serum sickness is a type of allergic reaction, which could potentially occur after receiving influenza vaccines. Symptoms include rash and joint pain, which usually resolves by itself or with treatment. Serum sickness related to influenza vaccine is considered very rare, and there is not enough information to determine if this reaction is definitely caused by influenza vaccines.
Accidental use of CSL's influenza vaccine in children under 5 years of age	CSL's influenza vaccine should not be used in children under 5 years of age (see Important Identified Risk: Fever and seizures/convulsions ('fits') in young children); however,

Risk	What is known (Including reason why it is considered a potential risk)
	there is the potential for healthcare professionals (e.g. GPs, nurses) to accidently use CSL's influenza vaccine in these patients.

Missing information

Risk	What is known
Limited information on use and safety of CSL's influenza vaccine in pregnant women	Pregnant women were not included in CSL's clinical trials. However, influenza vaccines have been used in many parts of the world for almost 50 years, including in pregnant women, and therefore the safety and efficacy of influenza vaccine in these women is well known. In addition, different government health bodies worldwide recommend pregnant women get the influenza vaccine, as they are considered to be at a higher risk of infection and potential complications from influenza.

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

These additional risk minimisation measures are for the following risks:

- **Fever and seizures/convulsions ('fits') in young children**
- **Accidental use of CSL's influenza vaccine in children under 5 years of age**

Risk minimisation measure(s): Inclusion of warnings on CSL's influenza vaccine packaging
Objective and rationale: To remind healthcare professionals (e.g. GPs, nurses) that CSL's influenza vaccine should not be used in children under 5 years of age
Summary of additional risk minimization measures: Include warnings that CSL's influenza vaccine should not be used in children under 5 years of age on the product packaging e.g. the outer box, the product packet, and/or on the actual product label

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
"Postmarketing Surveillance of Afluria® Influenza Vaccine Safety in Pregnancy"	To assess the magnitude of use of CSL TIV in US in pregnancy (exposure prevalence) and the risks associated with such use To monitor pregnancy outcomes (spontaneous abortions, preeclampsia, foetal deaths, preterm births, and intrauterine growth restriction) and congenital malformations (major and specific malformations)	Exposure and safety of CSL TIV in pregnancy (Missing information)	Started	Report submission annually to FDA from the start of recruitment (NH 2013/14 season) Study completion and submission of final report in 2017

There are no planned post authorisation efficacy studies for CSL TIV.

Studies which are a condition of the marketing authorisation

CSL voluntarily committed to establishing the pregnancy surveillance study for Afluria® (registered product name of CSL TIV in the US), as a condition of approval of supplement STN BL 125254/259.

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
Global RMP 1.0	November 2010	Important identified risks • Febrile convulsions/ febrile events in paediatric patients • Anaphylaxis Important potential risks • Encephalitis • Seizures/convulsions (non-febrile) • Guillain-Barré syndrome • Transverse myelitis • Optic neuritis • Bell's palsy • Serum sickness • Inadvertent use in children under 5 years of age Missing information • Exposure and safety of CSL TIV in pregnancy	First Global RMP written in accordance with the template published by the EMEA (EMEA/192632/2006). Minor local changes made to this version at the request of individual Regulatory Authorities
Global RMP 2.0	May 2012	See Global RMP 1.0	Additional risk minimisation activities to prevent *Inadvertent use in children under 5 years of age* and *Febrile convulsions/ febrile events in paediatric patients*
RMP 3.0 (submitted to EU only)	May 2014	See Global RMP 2.0	Transfer to new template published by the EMA (EMA/465932/2013) Update and conclusions of the scientific investigations into the SH 2010 adverse events. Information on the Post Authorisation Safety Study to address the new requirement of Enhanced Safety Surveillance for influenza virus vaccines. Data and conclusions from

Version	Date	Safety Concerns	Comment
			Pharmajet study. Information on the Pregnancy surveillance study
RMP 3.1 (submitted to EU only)	October 2014	See RMP 3.0 - addition of *other identified risks due to common pharmacological class effects* 'local and systemic adverse reactions (reactogenicity)' and 'allergic reactions' for the pilot PASS conducted in the NH 2014/15 season	Update to information on PASS
Global RMP 4.0	August 2015	See RMP 3.0 - minor wording update from *encephalitis* to *encephalomyelitis*, as per the recommendations from a safety signal evaluation described in PSUR 21 (DLP: 01-May-2014 to 31-Aug-2014) - removal of *other identified risks due to common pharmacological class effects* 'local and systemic adverse reactions (reactogenicity)' and 'allergic reactions' as these are not considered important identified/potential risks. Additionally, the results from the pilot PASS conducted in the NH 2014/15 season supports that these events are consistent with the known safety profile of CSL TIV.	Update to cumulative action taken for safety reasons for recent seasons Update to post-marketing exposure data Update to cumulative no. or medication error reports Update to cumulative no. of reports of identified & potential risks Removal of additional risk minimisation (RM) measure of DHPC. It is considered this measure is no longer required. Restriction of the indication to adults and children from 5 years; routine RM measures, including warnings in sections of the product label; and additional RM measures of warnings on the product packaging are considered effective for these safety concerns. Refer to Part V, V.1 of this RMP for details. Data and conclusions from CSLCT-USF-10-69 study Update and conclusions of the scientific investigations into the SH 2010 adverse events

Version	Date	Safety Concerns	Comment
			Update to information on PASS Update to information on pregnancy surveillance study
Global RMP 5.0	August 2016	See Global RMP 4.0	Update to product name throughout document (IVV to TIV) Update to include information on EPSS (replacing PASS) Update to clinical trial exposure data (CSLCT-QIV-13-01) Update to cumulative action taken for safety reasons for recent seasons Update to post-marketing exposure data Update to cumulative no. or medication error reports Update to cumulative no. of reports of identified & potential risks Update to studies and other activities completed since last update Minor additional wording and section updates
RMP 5.1 (submitted to EU only)	September 2017	See Global RMP 5.0	Inclusion on post-authorisation effectiveness study