Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Enzira Suspension for injection, pre-filled syringe
Influenza vaccine (split virion, inactivated)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus* (inactivated with β-Propiolactone, split) of the following strains:

A/Michigan/45/2015 (H1N1) pdm09 - like strain (A/Singapore/GP1908/2015, IVR-180A)	15 micrograms HA**
A/Singapore/INFIMH-16-0019/2016 (H3N2) - like strain (A/Singapore/INFIMH-16-0019/2016, IVR-186)	15 micrograms HA**
B/Colorado/06/2017 - like strain (B/Maryland/15/2016, wild type)	15 micrograms HA**

per 0.5 ml dose.

* propagated in fertilised hens' eggs from healthy chicken flocks
** haemagglutinin

This vaccine complies with the WHO recommendation (Northern Hemisphere) and EU decision for the 2018/2019 season.

For the full list of excipients, see section 6.1.

Enzira may contain traces of eggs such as ovalbumin and residues of neomycin and polymyxin, which are used during the manufacturing process (see section 4.3).

3 PHARMACEUTICAL FORM

Suspension for injection in a pre-filled syringe.
Clear to slightly opaque liquid with some sediment that resuspends upon shaking.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis of influenza, especially in those who run an increased risk of associated complications.

Enzira is indicated in adults and children from 5 years of age.
The use of Enzira should be based on official recommendations.

4.2 Posology and method of administration

Posology

Adults:	0.5 ml

Paediatric population

Children from 5 years onwards:	0.5 ml

For children aged less than 9 years, who have not previously been vaccinated, a second dose should be given after an interval of at least 4 weeks.

Method of administration
Immunisation should be carried out by intramuscular or deep subcutaneous injection.
For instructions for preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, or to any component that may be present as traces such as eggs (ovalbumin, chicken proteins), neomycin, polymyxin.

Immunisation shall be postponed in patients with febrile illness or acute infection.

4.4 Special warnings and precautions for use

Paediatric population
During the 2010 Southern Hemisphere influenza season, there was an unexpected increase in reports of fever and febrile convulsions in children aged less than 5 years following seasonal influenza vaccination with this product. Febrile convulsions were reported uncommonly (i.e. reporting frequency estimated to be in the range ≥1/1000 to < 1/100)*.
An increased number of reports of fever was also reported in the age group 5 to less than 9 years. Therefore in this age group a decision to vaccinate with Enzira should be based on careful consideration of potential benefits and risks in the individual.
On the basis of the increased risk of febrile convulsions in children less than 5 years of age, the vaccine indication has been restricted to use in adults and children from 5 years of age only.
(*estimated from epidemiological investigations)

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration of the vaccine.

Enzira should under no circumstances be administered intravascularly.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

Interference with serological testing
(See section 4.5)

4.5 Interaction with other medicinal products and other forms of interaction

Enzira may be given at the same time as other vaccines. Immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

Following influenza vaccination, false positive results in serological tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the false positive ELISA test results. The transient false positive reactions could be due to the IgM response by the vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy
Inactivated influenza 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 inactivated influenza vaccines do not indicate any adverse foetal and maternal outcomes attributable to the vaccine. An animal study conducted with Enzira did not indicate reproductive toxicity (see section 5.3).

Breastfeeding

Enzira may be used during breastfeeding.

Fertility
An animal study conducted with Enzira did not indicate adverse effects on female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Enzira has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions observed from clinical trials
Adult and Elderly populations
Summary of the safety profile
In clinical trials, a single dose of Enzira has been administered to, and safety information collected for, 11,104 adults aged 18 to less than 65 years and 630 elderly aged 65 years or older. Clinical data are presented from 3 clinical trials; two placebo-controlled trials in adults (CSLCT-FLU-05-09 and CSLCT-USF-06-28) and one comparator-controlled trial in elderly (CSLCT-USF-07-41).

The safety assessment was similar for the three trials. Local (injection-site) adverse reactions and systemic adverse events were solicited for 5 days after vaccination. Unsolicited adverse events were collected for 21 days after vaccination.

The frequency of solicited local adverse reactions and systemic adverse events, and related unsolicited adverse events, are presented according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and frequency for adults from 18 years of age (Table 1). Among the trials, there were no vaccine-related deaths or vaccine-related serious adverse events reported.

For adults and elderly, the most frequently reported related unsolicited adverse events across the three clinical trials were reactogenicity event (3.0%), headache (1.1%) and arthralgia (1.1%).

Tabulated list of adverse reactions
Table 1: Solicited local adverse reactions, solicited systemic adverse events and related unsolicited adverse events by MedDRA System Organ Class and category of frequency in adults 18 years of age and older

System Organ class	Very common >1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Nervous system disorders	Headache [a]	Headache [b,c]	
Gastrointestinal disorders		Nausea [a,b]	Vomiting [a,b]
Musculoskeletal and connective tissue disorders	Myalgia/general muscle ache [a]	Myalgia/general muscle ache [b] Arthralgia[c]	
General disorders and administration site conditions	Injection site tenderness [a,b] Injection site pain [a,b] Malaise [a]	Injection site erythema/ redness [a,b] Injection site swelling/ induration	Pyrexia/fever [b] Injection site ecchymosis/ bruising [b]

		[a,b] Chills/ shivering [a,b] Pyrexia/fever [a] Injection site ecchymosis/ bruising [a] Malaise [b] Reactogenicity event[c]	

No solicited local adverse reactions or systemic adverse events were categorized as Rare (≥1/10,000, <1/1,000), or Very rare (<1/10,000).

[a] Solicited local adverse reaction or systemic adverse event in adults 18 to < 65 years.

[b] Solicited local adverse reaction or systemic adverse event in elderly ≥ 65 years.

[c] Related unsolicited adverse event.

Paediatric population

Summary of the safety profile

In clinical trials, Enzira has been administered to, and safety information collected for, 3,009 children aged 6 months to less than 18 years. The exposure includes 1,601 children aged 6 months to less than 5 years, 756 children aged 5 years to less than 9 years and 652 children aged 9 years to less than 18 years. Clinical safety data for Enzira in children has been evaluated from 3 clinical trials; a comparator-controlled trial (CSLCT-USF-07-36) and two open label, uncontrolled trials (CSLCT-USF-06-29 and CSLCT-FLU-04-05). Children aged 6 months to less than 9 years received one or two vaccinations as determined by previous vaccination history.

The safety assessment was similar for the three paediatric trials. Local (injection site) and systemic adverse events were solicited for 7 days after vaccination. Unsolicited adverse events were collected for 30 days after vaccination.

In children aged 5 to less than 9 years who received Enzira in the comparator-controlled trial, the rate of malaise after dose 1 was 24% as compared to 13% who received the comparator, and the rate of diarrhoea after dose 2 was 13% as compared to 6% who received the comparator. In the same trial, the rate of fever after the first dose of Enzira in children aged 5 to less than 9 years was 16% as compared to 8% in children who received the comparator. The rate of fever in children aged 9 to less than 18 years following a single dose of Enzira was 6% as compared to 4% in children who received the comparator.

Across the paediatric clinical trials, erythema was reported more often in children 5 to less than 9 years compared to children 9 to less than 18 years after a single dose (23% vs 17% in the comparator-controlled trial; 24% vs 17% in the open label trials). In contrast, headache was less often reported in children 5 to less than 9 years compared to children 9 to less than 18 years after a single dose (21% vs 27% in the comparator-controlled trial; 16% vs 27% in the open label trials). In children 5 to less than 9 years, systemic adverse events were reported less often after dose 2 than dose 1. Among the paediatric trials, there were no vaccine-related deaths or vaccine-related serious adverse events reported in this age cohort.

The frequency of solicited local adverse reactions and systemic adverse events, and related unsolicited adverse events are presented according to the MedDRA System Organ Class and frequency (Table 2) for children 5 years of age and older, consistent with the current age indication for Enzira.

For children aged 5 to less than 9 years, the most frequently reported related unsolicited adverse events across the three clinical trials were cough (3.5%), upper respiratory tract infection (2.9%), rhinitis (2.2%) and rhinorrhoea (2.2%). For children aged 9 to less than 18 years, the most frequently reported related unsolicited adverse events across the three clinical trials were cough (2.8%), oropharyngeal pain (2.4%) and nasal congestion (2.4%).

Tabulated list of adverse reactions

Table 2: Solicited local adverse reactions, solicited systemic adverse events and related unsolicited adverse events by MedDRA System Organ Class and category of frequency in children aged 5 to less than 18 years

System Organ class	Very common >1/10	Common ≥1/100 to <1/10
Infections and infestations		Upper respiratory tract infection[c] Rhinitis[c] Nasopharyngitis[c]
Nervous system disorders	Headache	Headache[c]
Respiratory, thoracic and mediastinal disorders		Cough[c,d] Oropharyngeal pain[c,d] Nasal congestion[c] Rhinorrhoea[c] Pharyngolaryngeal Pain[c]
Gastrointestinal disorders		Nausea / vomiting [a] Diarrhoea [a] Loss of appetite [b] Vomiting/diarrhoea [b] Abdominal pain upper[c] Abdominal pain[c]
Musculoskeletal and connective tissue disorders	Myalgia/general muscle ache	
General disorders and administration site conditions	Injection site pain Injection site erythema/redness Malaise [a] Irritability [b] Injection site swelling/induration Pyrexia/fever	Injection site pruritis[c] Pyrexia[c] Influenza-like illness[c] Irritability[c]

No solicited local adverse reactions or systemic adverse events were categorized as Uncommon (≥1/1,000, <1/100), Rare(≥1/10,000, <1/1,000), or Very rare (<1/10,000).

[a] Solicited systemic adverse events collected in trials CSLCT-USF-07-36 and CSLCT-USF-06-29.

[b] Solicited systemic adverse events collected in trial CSLCT-FLU-04-05.

[c] Related unsolicited adverse event in children aged 5 to < 9 years.

[d] Related unsolicited adverse event in children aged 9 to < 18 years.

Adverse reactions reported from post-marketing surveillance

The following adverse events have been spontaneously reported during post-marketing use of Enzira and are in addition to the events observed during clinical trials. The adverse events reported are presented below according to

System Organ Class:

Blood and lymphatic system disorders:
Thrombocytopenia, transient lymphadenopathy

Immune system disorders:
Allergic or immediate hypersensitivity reactions including anaphylactic shock

Nervous system disorders:
Neuralgia, paraesthesia, convulsions (including febrile convulsions), encephalomyelitis, neuritis or neuropathy and Guillain-Barré syndrome

Vascular disorders:
Vasculitis which may be associated with transient renal involvement

Skin and subcutaneous tissue disorders:
Pruritus, urticaria and rash

General disorders and administration site conditions:
Cellulitis and large injection site swelling
Influenza-like illness

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overdosage is unlikely to have any untoward effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07B B02

Seroprotection is generally obtained within 2 to 3 weeks. The duration of postvaccinal immunity to homologous strains or to strains closely related to the vaccine strains varies, but is usually 6 to 12 months.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

In a reproductive and developmental toxicity study, the effect of Enzira on embryo-foetal and pre-weaning development was evaluated in pregnant rats. No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-foetal or pre-weaning development were observed. There were no vaccine-related foetal malformations or other evidence of teratogenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Anhydrous disodium phosphate
Sodium dihydrogen phosphate dihydrate
Potassium chloride
Potassium dihydrogen phosphate
Calcium chloride
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

15 months.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C). Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 ml suspension in pre-filled syringe (Type I glass) with plunger stopper (chlorobutyl rubber) with or without attached needle in pack sizes of 1 or 10. The syringe with attached needle may be supplied with or without needle-trap.***

Not all pack sizes may be marketed.

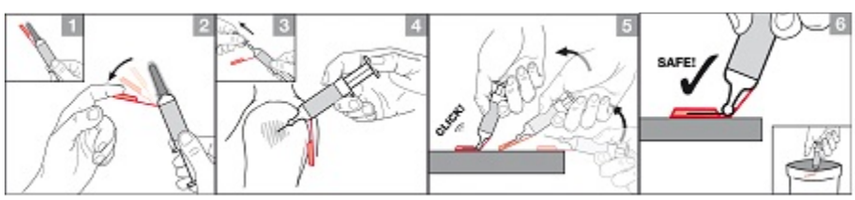
***See section 6.6 for instructions for use.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Shake before use. After shaking, the vaccine should appear as a homogenous suspension. The vaccine must be inspected visually prior to administration and should not be used if there is any variation of physical appearance (see section 3).

Enzira is presented as a single use syringe and any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For administration using the syringe with attached needle and needle-trap, refer to the diagrams below.



1-2: Bend the orange plastic needle-trap toward the side.
3-4: Remove the translucent plastic needle-shield cover and grey needle-shield and perform the injection. Intramuscular

administration of influenza vaccine should be undertaken by injection into the deltoid muscle of the upper arm.
5: Place the orange needle-trap against a stable, hard surface and then press down the trap by bending the syringe. Continue the motion until the needle is bent by approximately 90 degrees and the needle audibly clicks into the trap.
6: The needle is now secured for safe disposal in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Seqirus GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA1373/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd June 2007
Date of last renewal: 29th March 2009

10 DATE OF REVISION OF THE TEXT

August 2018