SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See Section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose, suspension for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus (inactivated, split) of the following strains*:

A/Michigan/45/2015 (H1N1) pdm09-like virus (A/Michigan/45/2015 X-275)
……60 micrograms HA**

A/Hong Kong/4801/2014 (H3N2)-like virus (A/Hong Kong/4801/2014 X-263B)
……60 micrograms HA**

B/Brisbane/60/2008-like virus (B/Brisbane/60/2008; Victoria lineage)
……60 micrograms HA**

Per 0.5 ml dose

* propagated in embryonated chicken eggs and inactivated with formaldehyde
** haemagglutinin

This vaccine complies with the WHO recommendations (Northern Hemisphere) and EU decision for the 2017/2018 season.

For the full list of excipients, see Section 6.1.

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose may contain traces of eggs, such as ovalbumin, formaldehyde and octoxinol-9, which are used during the manufacturing process (see Section 4.3). Neither antibiotics nor preservatives are used during manufacture.

3 PHARMACEUTICAL FORM

Suspension for injection, in a pre-filled syringe
Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose, after shaking gently, is essentially clear and opalescent in colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose is indicated for active immunisation in adults 65 years of age and older for the prevention of influenza disease.

The use of Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose should be based on official recommendations.

4.2 Posology and method of administration

Posology

Given the variation of the influenza viruses and the duration of immunity provided by the vaccine, it is recommended to perform vaccination against influenza every year**.**

In adults 65 years of age and older: one dose of 0.5 ml.

Paediatric population

Safety and effectiveness of Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose in those less than 18 years of age have not been established.

Method of administration

The vaccine should be given by intramuscular injection.

The recommended site for intramuscular injection is the deltoid region. The vaccine should not be injected into the gluteal region, or into areas where there may be a major nerve trunk.

For instructions on preparation of the medicinal product before administration, see Section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or 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), formaldehyde and octoxinol-9.

Vaccination shall be postponed in patients with moderate or severe febrile illness or acute infection.

4.4 Special warnings and precautions for use

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

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose should under no circumstances be administered intravascularly or subcutaneously.

As with other vaccines administered intramuscularly, the vaccine should be administered with caution to subjects with thrombocytopaenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose is intended to provide protection against those strains of influenza virus from which the vaccine is prepared or to closely related strains. As with any vaccine, vaccination with Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose may not protect all vaccinees.

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

4.5 Interaction with other medicinal products and other forms of interaction

There are no data to assess the concomitant administration of Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose with other vaccines.

If Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose needs to be given at the same time as another injectable vaccine(s), immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been reported. An appropriate Western Blot test should be used to confirm or disprove the results of the ELISA test. The transient false positive reactions could be due to a non-specific IgM response induced by influenza vaccine.

4.6 Fertility, pregnancy and lactation

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose is only indicated for use in adults aged 65 years and older.

Fertility

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose has not been evaluated for possible effects on human fertility.

Pregnancy

Animal reproductive studies have not been conducted with Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose. It is also not known whether Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity.

Data on the use of this vaccine in pregnant women are limited.

Breastfeeding

It is not known whether Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose is excreted in human milk.

4.7 Effects on ability to drive and use machines

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse event information is derived from clinical trials and post-marketing experience.

In total, 25,564 subjects have been exposed to Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose through its clinical development programme and post marketing clinical trials.

The most common reactions occurring after vaccine administration were injection-site reactions (pain, erythema and swelling) reported overall by 41.8% of study participants receiving Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose, and 31.3% of study participants receiving a standard dose trivalent influenza vaccine.

The most common reactions occurring after Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose administration were injection-site pain (35.6%), myalgia (21.4%), malaise (18.0%), headache (16.8%) and injection

site erythema (14.9%). The majority of these reactions occurred and resolved within three days of vaccination.

Local injection-site reactions (pain, erythema, swelling) and systemic adverse reactions (myalgia, malaise, headache, fever ≥37.5°**C**) were more frequent after vaccination with Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose compared to a standard dose vaccine.

b Tabulated list of adverse reactions

The data below summarise the frequencies of adverse reactions that were recorded following vaccination with Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose during the pivotal immunogenicity study (2,573 adults 65 years of age and older) and adverse reactions reported during post-marketing experience (*).

Adverse events are ranked under headings of frequency using the following convention:

Very common (≥1/10);

Common (≥1/100 to <1/10);

Uncommon (≥1/1,000 to <1/100);

Rare (≥1/10,000 to <1/1,000);

Very rare (<1/10,000);

Not known (cannot be estimated from available data).

ADVERSE REACTIONS	**FREQUENCY**
General Disorders and Administration Site Conditions	
Injection site pain, injection site erythema, malaise	Very common
Injection site swelling, fever (≥37.5°C)	Common
Chills, injection site bruising, injection site induration, fatigue	Uncommon
Asthenia, chest pain	Not known*
Musculoskeletal and Connective Tissue Disorders	
Myalgia	Very common
Pain in extremities	Uncommon
Arthralgia	Not known*
Nervous System Disorders	
Headache	Very common
Dizziness	Uncommon

ADVERSE REACTIONS	FREQUENCY
Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), neuritis, syncope (shortly after vaccination), paraesthesia	Not known*
Blood and Lymphatic System Disorders	
Lymphadenopathy	Uncommon
Thrombocytopenia	Not known*
Respiratory, thoracic and mediastinal disorders	
Cough	Uncommon
Dyspnoea, pharyngitis, rhinitis, wheezing, throat tightness	Not known*
Gastrointestinal Disorders	
Nausea, diarrhoea, vomiting	Uncommon
Immune System Disorders	
Pruritus	Rare
Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)	Not known*
Vascular disorders	
Flushing	Rare
Vasculitis, vasodilatation	Not known*
Eye Disorders	
Ocular hyperemia	Not known*

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 via the Medicines and Healthcare products Regulatory Agency (MHRA), Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Cases of administration of more than the recommended dose have been reported with Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose associated with inadvertent use in the population below 65 years of age due to medication error. When adverse reactions were reported, the

information was consistent with the known safety profile of Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB.

Mechanism of action

Influenza illness and its complications follow infection with influenza viruses.

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose induces humoral antibodies against the haemagglutinins within 2 to 3 weeks. These antibodies neutralise influenza viruses.

Specific levels of haemagglutination-inhibition (HAI) antibody titre post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HAI antibody titres have been used as a measure of vaccine activity. In some human challenge studies, HAI antibody titres of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.

Annual influenza vaccination is recommended because immunity during the year after vaccination declines and because circulating strains of influenza virus change from year to year.

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose was compared in two pivotal trials with the same vaccine containing the standard dose of 15 micrograms of each of the three strains [2 A strains and 1 B strain]) in adults 65 years of age and older.

Pivotal immunogenicity trial (FIM05)

FIM05 was a multi-centre, randomised, double-blind controlled trial conducted in the US. The objective of this study was to demonstrate the superiority of the High Dose versus a standard dose vaccine, as assessed by seroconversion rates and GMT ratios. High Dose vaccine elicited a superior immune response for the 2 A strains and showed a non-inferior immune response for the B strain, compared to the standard dose vaccine.

Table 1: Immunogenicity analysis 28 days post-vaccination in adults ≥ 65 years

	High Dose vaccine N=2576		**Standard dose vaccine N=1275**		
Seroconversion rates					
Influenza Strain	**n/M**	**SC rate % (95% CI)**	**n/M**	**SC rate[1] % (95% CI)**	**% Difference[2] TIV-HD minus TIV-SD (95% CI)**
H1N1	1229/2531	48.56 (46.59; 50.53)	289/1249	23.14 (20.83; 25.58)	25.42 (22.38; 28.46)
H3N2	1749/2531	69.10 (67.26; 70.90)	633/1248	50.72 (47.91; 53.53)	18.38 (15.08; 21.69)
B	1056/2529	41.76 (39.82; 43.71)	374/1249	29.94 (27.41; 32.57)	11.81 (8.63; 15.00)
GMT ratios					
Influenza Strain	**M**	**GMT (95% CI)**	**M**	**GMT (95% CI)**	**GMTR[3] TIV-HD/TIV-SD (95% CI)**
H1N1	2543	115.79 (111.41; 120.34)	1252	67.29 (63.65; 71.13)	1.72 (1.61; 1.84)
H3N2	2544	608.87 (583.54; 635.30)	1252	332.46 (310.44; 356.05)	1.83 (1.70; 1.98)
B	2542	69.06 (66.60; 71.60)	1252	52.34 (49.48; 55.35)	1.32 (1.24; 1.41)

N is the number of subjects in the Immunogenicity Analysis Set

n is the number of subjects who achieved seroconversion for each strain

M is the number of subjects with both pre- and post-vaccination serology results for the strain (seroconversion), or a valid serology result (GMT), including results reported as <LLOQ (lower limit of quantification)

[1] Seroconversion: For subjects with a Day 0 pre-vaccination titre <10 (1/dil): Titre ≥40 (1/dil) on Day 28; for subjects with a Day 0 pre-vaccination titre ≥10 (1/dil): ≥4-fold increase in titre on Day 28

[2] Superiority for a virus strain: the lower limit of the 95% CI for the difference of the seroconversion rates (HD minus SD) is >10%

[3] Superiority for a virus strain: the lower limit of the 95% CI for GMT ratio (HD/SD) is >1.5

Pivotal efficacy trial (FIM12)

FIM12 was a multi-centre, double-blind efficacy trial conducted in the US and Canada in which subjects were randomised (1:1) to receive the High Dose or a standard dose vaccine. The study was conducted over two influenza seasons (2011-2012 and 2012-2013) to assess the occurrence of laboratory-confirmed influenza caused by any influenza viral type/subtype, in association with influenza-like illness (ILI) as the primary endpoint.

Participants were monitored for the occurrence of a respiratory illness by both active and passive surveillance, starting 2 weeks post-vaccination for approximately 7 months. After an episode of respiratory illness, nasopharyngeal swab samples were collected for analysis; attack rates and vaccine efficacy were calculated. The pre-specified statistical superiority criterion for the primary endpoint (lower limit of the 2-sided 95% CI of the vaccine efficacy for the High Dose relative to standard dose vaccine > 9.1%) was met.

Table 2: Relative vaccine efficacy to prevent influenza-like illness[a] in adults ≥ 65 years

	High Dose vaccine N[b]=15,892 n[c] (%)	**Standard dose vaccine N[b]=15,911 n[c] (%)**	**Relative Efficacy % (95% CI)**
Laboratory-confirmed influenza[d] caused by:			
- **Any type/subtype[e]**	227 (1.43)	300 (1.89)	24.2 (9.7; 36.5)
- **Viral strains similar to those contained in the vaccine**	73 (0.46)	113 (0.71)	35.3 (12.4; 52.5)

[a]Occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrent with at least one of the following systemic signs or symptoms: temperature >37.2°C, chills, tiredness, headaches or myalgia

[b]N is the number of vaccinated participants in the per-protocol analysis set for efficacy assessments

[c]n is the number of participants with protocol-defined influenza-like illness with laboratory confirmation

[d]Laboratory-confirmed: culture- or polymerase-chain-reaction-confirmed

[e]Primary endpoint

Effectiveness studies

Randomised clinical trial

A cluster-randomised controlled trial was performed in 53, 008 US nursing home residents aged 65 years and older during the 2013-14 influenza season, using Medicare claims *(Gravenstein S et al., Lancet Respir Med, 2017;5(9):738-46).* The incidence of hospital admissions for respiratory illness (primary outcome) was significantly reduced by 12.7% (p=0.023) in the group of residents who received the High Dose vaccine compared to residents in the standard dose vaccine group. High Dose vaccine also significantly reduced hospital admissions for pneumonia by 20.9% (p=0.013) and all-cause hospital admissions by 8.5% (p=0.0028), when compared with standard dose vaccine.

Observational studies

Effectiveness of High Dose versus standard dose vaccines was assessed in a retrospective database study among 6 million US Medicare beneficiaries vaccinated in community pharmacies during 2 influenza seasons *(Shay DK et al, J Infect Dis, 2017;215:510-7).* The primary outcome was post-influenza death, defined as a death occurring in the 30 days following a Medicare claim for an in-patient hospitalisation or an emergency department visit, with a diagnosis of influenza. Overall, High Dose vaccine was 24.0% (95% CI: 0.6 to 41.8) more effective in preventing post-influenza death and also 18.6 % (95% CI, 14.1 to 22.9) more effective in preventing hospitalisation for influenza than standard dose influenza vaccines over both seasons (2012-2013 and 2013-2014) combined.

A retrospective, matched, cohort study of Veterans Health Administration patients 65 years and older during the 2015-2016 influenza season *(Young Xu et al, J Infect Dis., 2018;217(11):1718-27),* showed a relative vaccine effectiveness of High dose (n=24,682) versus standard dose vaccines (n=49,091) of 25% (95% CI, 2 to 43%) at preventing hospitalisation with underlying influenza or pneumonia diagnosis (primary outcome).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Trivalent Influenza Vaccine (Split Virion, Inactivated) High Dose has not been evaluated in non-clinical studies. It has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Diluent: Sodium phosphate-buffered isotonic sodium chloride solution (Sodium chloride, Monobasic sodium phosphate, Dibasic sodium phosphate, Water for injection)

Excipient: octoxinol-9

6.2 Incompatibilities

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

6.3 Shelf life

9 months

6.4 Special precautions for storage

Store in a refrigerator (2°C - 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 of suspension in pre-filled syringe (Type I glass) without needle, equipped with a plunger stopper (bromobutyl rubber) – pack size of 5 or 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The vaccine should be allowed to reach room temperature before use.
Shake before use.
Intramuscular vaccines should be inspected visually for particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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