

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

Quadrivalent Influenza Vaccine (split virion, inactivated), suspension for injection in pre-filled syringe
Quadrivalent influenza vaccine (split virion, inactivated)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

| | |
|--|-----------------------|
| A/Michigan/45/2015 (H1N1)pdm09 - like strain (A/Michigan/45/2015, NYMC X-275) | ...15 micrograms HA** |
| A/Hong Kong/4801/2014 (H3N2) - like strain (A/Hong Kong/4801/2014, NYMC X-263B) | ...15 micrograms HA** |
| B/Brisbane/60/2008 - like strain (B/Brisbane/60/2008, wild type) | ...15 micrograms HA** |
| B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, 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 recommendations (Northern Hemisphere) and EU decision for the 2017/2018 season.

For the full list of excipients, see Section 6.1.

Quadrivalent Influenza Vaccine (split virion, inactivated) may contain traces of eggs, such as ovalbumin, and of neomycin, formaldehyde and octoxinol-9, which are used during the manufacturing process (see Section 4.3).

3 PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.
The vaccine, after shaking gently, is a colourless opalescent liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Quadrivalent Influenza Vaccine (split virion, inactivated) is indicated for active immunisation of adults and children from 3 years of age and older for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.

The use of Quadrivalent Influenza Vaccine (split virion, inactivated) should be based on official recommendations.

4.2 Posology and method of administration

Posology

Based on clinical experience with the trivalent vaccine, annual revaccination with influenza vaccine is recommended given the duration of immunity provided by the vaccine and because circulating strains of influenza virus might change from year to year.

Adults: one dose of 0.5 ml.

Paediatric population

- Children from 3 years to 17 years of age: one dose of 0.5 ml.

For children less than 9 years of age who have not previously been vaccinated, a second dose of 0.5 ml should be given after an interval of at least 4 weeks.

- Children less than 3 years of age: the safety and efficacy of Quadrivalent Influenza Vaccine (split virion, inactivated) have not yet been established.

Method of administration

The vaccine should be given by intramuscular or subcutaneous injection.

The recommended site for intramuscular injection is the deltoid region.

Precautions to be taken before handling or administering the medicinal product

For instructions on 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, formaldehyde and octoxinol-9.

Vaccination should be postponed in case of moderate or severe febrile disease or acute disease.

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.

Quadrivalent Influenza Vaccine (split virion, inactivated) should under no circumstances be administered intravascularly.

As with other vaccines administered intramuscularly, the vaccine should be administered with caution to subjects with thrombocytopenia 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.

Quadrivalent Influenza Vaccine (split virion, inactivated) is intended to provide protection against those strains of influenza virus from which the vaccine is prepared.

As with any vaccine, vaccination with Quadrivalent Influenza Vaccine (split virion, inactivated) may not protect all vaccinees.

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

No interaction studies have been performed with Quadrivalent Influenza Vaccine (split virion, inactivated).

Quadrivalent Influenza Vaccine (split virion, inactivated) can be given at the same time as other vaccines, based on clinical experience with Vaxigrip. Separate injection sites and separate syringes should be used in case of concomitant administration.

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 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 lactationPregnancy

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.

There are no data on the use of Quadrivalent Influenza Vaccine (split virion, inactivated) in pregnant women.

One animal study with Quadrivalent Influenza Vaccine (split virion, inactivated) did not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development or early post-natal development.

Breastfeeding

Quadrivalent Influenza Vaccine (split virion, inactivated) may be used during breastfeeding.

Fertility

There are no fertility data available in Humans. One animal study with Quadrivalent Influenza Vaccine (split virion, inactivated) did not indicate harmful effects on female fertility.

4.7 Effects on ability to drive and use machines

Quadrivalent Influenza Vaccine (split virion, inactivated) has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects**a. Summary of the safety profile**

The safety of Quadrivalent Influenza Vaccine (split virion, inactivated) was assessed in five clinical trials in which 3040 adults from 18 to 60 years of age, 1392 elderly over 60 years of age and 429 children from 9 to 17 years of age received one dose of Quadrivalent Influenza Vaccine (split virion, inactivated) and 884 children from 3 to 8 years of age received one or two doses of Quadrivalent Influenza Vaccine (split virion, inactivated) depending on their influenza vaccination history.

In all of these trials, the comparator vaccine was Inactivated Influenza Vaccine (Split Virion) BP, Sanofi Pasteur trivalent inactivated influenza vaccine.

The overall safety profile of Quadrivalent Influenza Vaccine (split virion, inactivated) was comparable to Inactivated Influenza Vaccine (Split Virion) BP.

Most reactions usually occurred within the first 3 days following vaccination, resolved spontaneously within 1 to 3 days after onset. The intensity of these reactions was mild.

The most frequently reported adverse reaction after vaccination, in all populations, was injection site pain (between 52.8% and 56.5% in children from 3 to 17 years of age and in adults and 25.8% in elderly).

The other most frequently reported adverse reactions after vaccination were:

- In adults: headache (27.8%), myalgia (23%) and malaise (19.2%),
- In elderly: headache (15.6%) and myalgia (13.9%),
- In children from 9 to 17 years of age: myalgia (29.1%), headache (24.7%), malaise (20.3%) and injection site swelling (10.7%),
- In children from 3 to 8 years of age: malaise (30.7%), myalgia (28.5%), headache (25.7%), injection site swelling (20.5%), injection site erythema (20.4%), injection site induration (16.4%), shivering (11.2%).

Overall, adverse reactions were generally less frequent in the elderly than in adults and children from 3 to 17 years of age.

b. Tabulated summary of adverse reactions

The data below summarize the frequencies of the adverse reactions that were recorded following vaccination with Quadrivalent Influenza Vaccine (split virion, inactivated) during clinical trials.

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).

Adult and elderly

The safety profile presented below is based on data from 3040 adults from 18 to 60 years of age and 1392 elderly over 60 years of age.

| ADVERSE REACTIONS | FREQUENCY |
|--|-------------|
| <i>Blood and Lymphatic System Disorders</i> | |
| Lymphadenopathy ⁽¹⁾ | Uncommon |
| <i>Immune System Disorders</i> | |
| Hypersensitivity ⁽¹⁾ , allergic reactions such as erythema, urticaria ⁽¹⁾ , pruritus ⁽²⁾ , pruritus generalised ⁽¹⁾ , dermatitis allergic ⁽¹⁾ , angioedema ⁽¹⁾ | Rare |
| <i>Nervous System Disorders</i> | |
| Headache | Very common |
| Dizziness ⁽³⁾ | Uncommon |
| Somnolence, paresthesia | Rare |
| <i>Vascular disorders</i> | |
| Hot flush ⁽⁴⁾ | Uncommon |
| <i>Respiratory, thoracic and mediastinal disorders</i> | |

| | |
|---|-------------|
| Dyspnoea ⁽¹⁾ | Rare |
| <i>Gastrointestinal Disorders</i> | |
| Diarrhoea, nausea ⁽⁵⁾ | Uncommon |
| <i>Skin and Subcutaneous System Disorders</i> | |
| Hyperhidrosis | Rare |
| <i>Musculoskeletal and Connective Tissue Disorders</i> | |
| Myalgia | Very common |
| Arthralgia ⁽¹⁾ | Rare |
| <i>General Disorders and Administration Site Conditions</i> | |
| Malaise ⁽⁶⁾ | Very common |
| Injection site pain | |
| Shivering, fever ⁽²⁾ | Common |
| Injection site erythema, injection site swelling, injection site induration | |
| Fatigue | Uncommon |
| Injection site ecchymosis, injection site pruritus, injection site warmth | |
| Asthenia, flu-like illness | Rare |
| Injection site discomfort ⁽¹⁾ | |

⁽¹⁾ In adults ⁽²⁾ Uncommon in elderly ⁽³⁾ Rare in adults ⁽⁴⁾ In elderly
⁽⁵⁾ Rare in elderly ⁽⁶⁾ Common in elderly

Paediatric population

The safety profile presented below is based on data from 429 children from 9 to 17 years of age who received one dose of Quadrivalent Influenza Vaccine (split virion, inactivated) and from 884 children from 3 to 8 years of age who received one or two doses of Quadrivalent Influenza Vaccine (split virion, inactivated) depending on their influenza vaccination history.

| ADVERSE REACTIONS | FREQUENCY |
|--|-------------|
| <i>Blood and Lymphatic System Disorders</i> | |
| Thrombocytopenia ⁽¹⁾ | Uncommon |
| <i>Psychiatric disorders</i> | |
| Moaning ⁽²⁾ , restlessness ⁽²⁾ | Uncommon |
| <i>Nervous System Disorders</i> | |
| Headache | Very common |
| Dizziness ⁽²⁾ | Uncommon |
| <i>Gastrointestinal Disorders</i> | |
| Diarrhoea, vomiting ⁽²⁾ , abdominal pain upper ⁽²⁾ | Uncommon |
| <i>Musculoskeletal and Connective Tissue Disorders</i> | |
| Myalgia | Very common |
| Arthralgia ⁽²⁾ | Uncommon |
| <i>General Disorders and Administration Site Conditions</i> | |
| Malaise, shivering ⁽³⁾ Injection site pain, injection site swelling, injection site erythema ⁽³⁾ , injection site induration ⁽³⁾ | Very common |
| Fever Injection site ecchymosis | Common |
| | |

| | |
|---|----------|
| Fatigue ⁽²⁾ , Injection site warmth ⁽²⁾ , injection site pruritus ⁽⁴⁾ | Uncommon |
|---|----------|

- ⁽¹⁾ Reported in one child of 3 years of age
- ⁽²⁾ Reported in children from 3 to 8 years of age
- ⁽³⁾ Common in children from 9 to 17 years of age
- ⁽⁴⁾ Reported in children from 9 to 17 years of age

In children from 3 to 8 years of age, the safety profile of Quadrivalent Influenza Vaccine (split virion, inactivated) was similar after the first and the second injections.

c. Potential adverse events

There are no safety data from post-marketing experience with Quadrivalent Influenza Vaccine (split virion, inactivated). However, the following adverse reactions have been reported with Inactivated Influenza Vaccine (Split Virion) BP during clinical trials or from post-marketing experience and may occur in people receiving Quadrivalent Influenza Vaccine (split virion, inactivated).

Immune system disorders

Severe allergic reactions: shock
Allergic reactions: rash, generalized erythema

Nervous system disorders

Guillain-Barre Syndrome (GBS), neuritis, neuralgia, convulsions, encephalomyelitis

Vascular disorders

Vasculitis, such as Henoch-Schonlein purpura, with transient renal involvement in certain cases

d. Other special populations

Safety profile of Quadrivalent Influenza Vaccine (split virion, inactivated) observed in limited number of subjects with co-morbidities enrolled in the clinical studies does not differ from the one observed in the overall population. In addition, studies conducted with Inactivated Influenza Vaccine (Split Virion) BP in renal transplant patients, and asthmatic patients showed no major differences in terms of safety profile of Inactivated Influenza Vaccine (Split Virion) BP in these populations.

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 Health Products Regulatory Authority (HPRA) at 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

Not documented for Quadrivalent Influenza Vaccine (split virion, inactivated). Cases of administration of more than the recommended dose (overdose) have been reported with Inactivated Influenza Vaccine (Split Virion) BP. When adverse reactions were reported, the information was consistent with the known safety profile of Inactivated Influenza Vaccine (Split Virion) BP.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02.

Mechanism of action

Quadrivalent Influenza Vaccine (split virion, inactivated) provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine.

Quadrivalent Influenza Vaccine (split virion, inactivated) induces humoral antibodies against the haemagglutinins within 2 to 3 weeks. These antibodies neutralise influenza viruses.

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

Since influenza viruses constantly evolve, the virus strains selected in the vaccine are reviewed annually by the WHO. Annual revaccination with Quadrivalent Influenza Vaccine (split virion, inactivated) has not been studied. However, based on clinical experience with the trivalent vaccine, annual influenza vaccination is recommended given the duration of immunity provided by the vaccine and because circulating strains of influenza virus change from year to year.

Immunogenicity of Quadrivalent Influenza Vaccine (split virion, inactivated) versus Inactivated Influenza Vaccine (Split Virion) BP

Clinical studies performed in adults from 18 to 60 years of age, in elderly over 60 years of age and in children 3 to 8 years of age assessed the non-inferiority of Quadrivalent Influenza Vaccine (split virion, inactivated) versus Inactivated Influenza Vaccine (Split Virion) BP for HAI Geometric mean antibody titer (GMT) at Day 21 (for adults) and at Day 28 (for children), HAI seroconversion rate (4-fold rise in reciprocal titer or change from undetectable [< 10] to a reciprocal titer of ≥ 40), and HAI GMT ratio (post-/pre-vaccination titers).

One clinical study performed in adults from 18 to 60 years of age and in children from 9 to 17 years of age described the immune response of Quadrivalent Influenza Vaccine (split virion, inactivated) versus Inactivated Influenza Vaccine (Split Virion) BP for HAI Geometric mean antibody titer (GMT) at Day 21. Another clinical study performed in children from 9 to 17 years of age described only the immune response of Quadrivalent Influenza Vaccine (split virion, inactivated).

Quadrivalent Influenza Vaccine (split virion, inactivated) induced a significant immune response to the 4 influenza strains contained in the vaccine.

In all studies, the immune response elicited by Quadrivalent Influenza Vaccine (split virion, inactivated) against the three strains in common was as immunogenic as Inactivated Influenza Vaccine (Split Virion) BP.

Quadrivalent Influenza Vaccine (split virion, inactivated) elicited a superior immune response against the additional B strain included in Quadrivalent Influenza Vaccine (split virion, inactivated) compared to Inactivated Influenza Vaccine (Split Virion) BP.

Adults and elderly

A total of 1114 adults from 18 to 60 years of age and 1111 elderly over 60 years of age received either one dose of Quadrivalent Influenza Vaccine (split virion, inactivated) or one dose of Inactivated Influenza Vaccine (Split Virion) BP.

Immunogenicity results are presented in the tables below:

Table 1: Immunogenicity results in adults aged from 18 to 60 years

| | Quadrivalent | Alternative Inactivated Influenza Vaccine (Split | Licensed Inactivated Influenza Vaccine |
|--|--------------|--|--|
|--|--------------|--|--|

| Antigen Strain | Influenza Vaccine (split virion, inactivated) N=832 | Virion) BP ^(a) (B Victoria) N=140 | (Split Virion) BP ^(b) (B Yamagata) N=138 |
|------------------------------------|--|--|---|
| GMT (95% CI) | | | |
| A (H1N1) ^{(c)(d)} | 608 (563;657) | 685 (587; 800) | |
| A (H3N2) ^(c) | 498 (459; 541) | 629 (543; 728) | |
| B (Victoria) | 708 (661; 760) | 735 (615; 879) | 204 (170; 243) |
| B (Yamagata) | 1715 (1607; 1830) | 689 (556; 854) | 1735 (1490; 2019) |
| SC or SI % (95% CI) ^(e) | | | |
| A (H1N1) ^{(c)(d)} | 64.1 (60.7; 67.4) | 65.1 (59.2; 70.7) | |
| A (H3N2) ^(c) | 66.2 (62.9; 69.4) | 73.4 (67.8; 78.5) | |
| B (Victoria) | 70.9 (67.7; 74.0) | 70.0 (61.7; 77.4) | 38.4 (30.3; 47.1) |
| B (Yamagata) | 63.7 (60.3;67.0) | 42.1 (33.9; 50.8) | 60.9 (52.2; 69.1) |
| GMTR (95% CI) ^(f) | | | |
| A (H1N1) ^{(c)(d)} | 9.77 (8.69; 11.0) | 10.3 (8.35; 12.7) | |
| A (H3N2) ^(c) | 10.3 (9.15; 11.5) | 14.9 (12.1; 18.4) | |
| B (Victoria) | 11.6 (10.4; 12.9) | 11.4 (8.66; 15.0) | 3.03 (2.49; 3.70) |
| B (Yamagata) | 7.35 (6.66;8.12) | 3.22 (2.67; 3.90) | 6.08 (4.79; 7.72) |

N=number of subjects with available data for the considered endpoint

GMT: Geometric Mean Titer; GMTR: Geometric Mean Titer Ratio; CI: Confidence Interval; SC: Seroconversion; SI: Significant Increase

- (a) Alternative TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage)
- (b) 2014-2015 licensed TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachussetts/2/2012 (Yamagata lineage)
- (c) Pooled TIV group includes participants vaccinated with either alternative Inactivated Influenza Vaccine (Split Virion) BP or licensed Inactivated Influenza Vaccine (Split Virion) BP, N=278
- (d) N=833 for Quadrivalent Influenza Vaccine (split virion, inactivated) group
- (e) For subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer
- (f) Geometric mean of individual ratios (post-/pre-vaccination titers)

Table 2: Immunogenicity results in elderly over 60 years of age

| Antigen Strain | Quadrivalent Influenza Vaccine (split virion, inactivated) N=831 | Alternative Inactivated Influenza Vaccine (Split Virion) BP ^(a) (B Victoria) N=138 | Licensed Inactivated Influenza Vaccine (Split Virion) BP ^(b) (B Yamagata) N=137 |
|-----------------------------|--|---|--|
| GMT (95% CI) | | | |
| A (H1N1) ^{(c) (d)} | 219 (199; 241) | 268 (228; 314) | |
| A (H3N2) ^(c) | 359 (329; 391) | 410 (352; 476) | |
| B (Victoria) | 287 (265; 311) | 301 (244; 372) | 121 (101; 147) |

| | | | |
|---|-------------------|-------------------|-------------------|
| B (Yamagata) | 655 (611; 701) | 351 (294; 420) | 697 (593; 820) |
| SC or SI % (95% CI) ^(e) | | | |
| A (H1N1) ^{(c) (d)} | 45.6 (42.1; 49.0) | 50.2 (44.1; 56.2) | |
| A (H3N2) ^(c) | 47.5 (44.1; 51.0) | 48.5 (42.5;54.6) | |
| B (Victoria) | 45.2 (41.8; 48.7) | 43.5 (35.1; 52.2) | 21.2 (14.7; 29.0) |
| B (Yamagata) | 42.7 (39.3; 46.2) | 28.3 (20.9; 36.5) | 38.7 (30.5; 47.4) |
| GMTR (95% CI) ^(f) | | | |
| A (H1N1) ^{(c) (d)} | 4.94 (4.46; 5.47) | 6.03 (4.93; 7.37) | |
| A (H3N2) ^(c) | 5.60 (5.02; 6.24) | 5.79 (4.74; 7.06) | |
| B (Victoria) | 4.61 (4.18; 5.09) | 4.60 (3.50; 6.05) | 1.99 (1.70; 2.34) |
| B (Yamagata) | 4.11 (3.73; 4.52) | 2.04 (1.71; 2.43) | 4.11 (3.19; 5.30) |

N=number of subjects with available data for the considered endpoint

GMT: Geometric Mean Titer; GMTR: Geometric Mean Titer Ratio; CI: Confidence Interval; SC: Seroconversion; SI: Significant Increase

- (a) Alternative TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage)
- (b) 2014-2015 licensed TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachussetts/2/2012 (Yamagata lineage)
- (c) Pooled TIV group includes participants vaccinated with either alternative Inactivated Influenza Vaccine (Split Virion) BP or licensed Inactivated Influenza Vaccine (Split Virion) BP, N=275
- (d) N=832 for Quadrivalent Influenza Vaccine (split virion, inactivated) group
- (e) For subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer
- (f) Geometric mean of individual ratios (post-/pre-vaccination titers)

Paediatric population

- Children aged from 9 to 17 years:
In a total of 429 children from 9 to 17 years of age who received one dose of Quadrivalent Influenza Vaccine (split virion, inactivated), the immune response against the 4 strains contained in the vaccine was similar to the immune response induced in adults 18 to 60 years of age.

- Children from 3 to 8 years of age:
A total of 1242 children 3 to 8 years of age received either one or two doses of Quadrivalent Influenza Vaccine (split virion, inactivated) or Inactivated Influenza Vaccine (Split Virion) BP depending on their previous influenza vaccination history.
Children who received a one- or two-dose schedule of Quadrivalent Influenza Vaccine (split virion, inactivated) presented a similar immune response following the last dose of the respective schedule.Immunogenicity results are presented in the table below:

Table 3: Immunogenicity results in children aged from 3 to 8 years

| Antigen Strain | Quadrivalent Influenza Vaccine (split virion, inactivated) N=863 | Alternative Inactivated Influenza Vaccine (Split Virion) BP ^(a) (B Victoria) N=176 | Licensed Inactivated Influenza Vaccine (Split Virion) BP ^(b) (B Yamagata) N=168 |
|---------------------|---|--|---|
| GMT (95% CI) | | | |
| | 971 (896; 1052) | 1141 (1006; 1295) | |

| | | | |
|------------------------------------|-------------------|-------------------|-------------------|
| A (H1N1) ^(c) | | | |
| A (H3N2) ^(c) | 1568 (1451; 1695) | 1746 (1551; 1964) | |
| B (Victoria) ^(d) | 1050 (956; 1154) | 1120 (921; 1361) | 170 (125; 232) |
| B (Yamagata) ^(e) (f) | 1173 (1078; 1276) | 217 (171; 276) | 1211 (1003; 1462) |
| SC or SI % (95% CI) ^(g) | | | |
| A (H1N1) ^(c) | 65.7 (62.4; 68.9) | 65.7 (60.4; 70.7) | |
| A (H3N2) ^(c) | 64.8 (61.5; 68.0) | 67.7 (62.5; 72.6) | |
| B (Victoria) ^(d) | 84.8 (82.3; 87.2) | 90.3 (85.0; 94.3) | 38.5 (31.1; 46.2) |
| B (Yamagata) ^(e) (f) | 88.5 (86.2; 90.6) | 46.0 (38.4; 53.7) | 89.9 (84.3; 94.0) |
| GMTR (95% CI) ^(h) | | | |
| A (H1N1) ^(c) | 6.86 (6.24; 7.53) | 7.65 (6.54; 8.95) | |
| A (H3N2) ^(c) | 7.49 (6.72; 8.35) | 7.61 (6.69; 9.05) | |
| B (Victoria) ^(d) | 17.1 (15.5; 18.8) | 17.8 (14.5; 22.0) | 3.52 (2.93; 4.22) |
| B (Yamagata) ^(e) (f) | 25.3 (22.8; 28.2) | 4.60 (3.94; 5.37) | 30.4 (23.8; 38.4) |

N=number of subjects with available data for the considered endpoint

GMT: Geometric Mean Titer; GMTR: Geometric Mean Titer Ratio; CI: Confidence Interval; SC: Seroconversion; SI: Significant Increase

- (a) Alternative TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Brisbane/60/2008 (Victoria lineage)
- (b) 2014-2015 licensed TIV containing A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachussetts/2/2012 (Yamagata lineage)
- (c) Pooled TIV group includes participants vaccinated with either alternative Inactivated Influenza Vaccine (Split Virion) BP or licensed Inactivated Influenza Vaccine (Split Virion) BP, N=344
- (d) N=169 for Inactivated Influenza Vaccine (Split Virion) BP (B Yamagata) group
- (e) N=862 for Quadrivalent Influenza Vaccine (split virion, inactivated) group
- (f) N=175 for Inactivated Influenza Vaccine (Split Virion) BP (B Victoria) group
- (g) For subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer
- (h) Geometric mean of individual ratios (post-/pre-vaccination titers)

The European Medicines Agency has deferred the obligation to submit the results of studies with Quadrivalent Influenza Vaccine (split virion, inactivated) in one or more subsets of the paediatric population in the prevention of influenza infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeat dose and local toxicity, reproductive and developmental toxicity and safety pharmacology studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Buffer Solution:
- Sodium chloride
 - Potassium chloride
 - Disodium phosphate dihydrate
 - Potassium dihydrogen phosphate
 - Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

1 year

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) with attached needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) – pack size of 1, 10 or 20.

0.5 ml of suspension in pre-filled syringe (type I glass) without needle, equipped with a plunger stopper (elastomer chlorobutyl or bromobutyl) – pack size of 1, 10 or 20.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use.

Shake before use. Inspect visually prior to administration.

The vaccine should not be used if foreign particles are present in the suspension.

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

7 MARKETING AUTHORISATION HOLDER

Sanofi Pasteur Europe
 2 Avenue Pont Pasteur
 69007 Lyon
 France

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th July 2016

10 DATE OF REVISION OF THE TEXT

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