For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

WHO recommendation strains for 2024 – 2025 (Northern hemisphere)

1. NAME OF THE MEDICINAL PRODUCT.

Inactivated Influenza Vaccine (Split Virion) I.P. (Tetravalent)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 ml contains:

A/Victoria/4897/2022 (H1N1) pdm09 – like virus	≥ 15 µg HA*
A/Thailand/8/202 (H3N2) – like virus	≥ 15 µg HA*
B/Austria/1359417/2021 (B/Victoria lineage) – like virus	≥ 15 µg HA*
B/Phuket/3073/2013 (B/Yamagata lineage) – like virus	≥ 15 µg HA*

Propagated in fertilized hen's eggs from healthy chicken flocks Inactivated by Beta propiolactone.
*Haemagglutinin.

3. PHARMACEUTICAL FORM

Liquid (Single dose) vaccine for intramuscular route of administration

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VaxiFlu™ – 4 is indicated in Children from 6 months to 17 years and adults ≥ 18 years of age for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Vaccination is particularly recommended for:

- Persons aged ≥ 65 years, regardless of their health condition
- All children below 5 years of age starting from 6 months of age annually (2-4 weeks before influenza season) as per IAP ACVIP 2020.
- Adults and Children with chronic disorders of the pulmonary or cardiovascular system, including asthma.

- Adults and Children with chronic metabolic disorders such as diabetes mellitus.
- Adults and Children with chronic renal dysfunction
- Adults and Children with immunodeficiency due to disease or immunosuppressive medication or radiotherapy.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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.

Dose and Schedule for VaxiFlu™ – 4:

Age	Dose	Schedule
6 months through 35 months	One or two doses*, 0.5 ml each	If 2 doses, administer at least 4 weeks apart
3 years through 8 years	One or two doses*, 0.5 ml each	If 2 doses, administer at least 4 weeks apart
9 years and older	One dose, 0.5 ml	----
*1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines		

Children less than 6 months of age: the safety and efficacy of Inactivated Tetravalent Influenza Vaccine (Split Virion) I.P. have not been established. No data are available.

The vaccine should be given by intramuscular injection. The preferred sites for intramuscular injection are the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in children 6 months through 35 months of age, or the deltoid muscle in children from 36 months of age and adults. Do not administer this product intravenously or intradermally. Shake well before administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

4.3 Contraindications

VaxiFlu™ – 4 is contraindicated in person with history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine. Immunization shall be postponed in patients with acute febrile illness.

4.4 Special warnings and precautions for use

The vaccine should under no circumstances be administered intravascularly.

In rare cases anaphylactic shock may occur in susceptible individual and for such emergency 1:1000 adrenaline injection should be kept ready to be injected intramuscularly or subcutaneously. For treatment of severe anaphylaxis, the initial dose of adrenaline is 0.1-0.5 mg (0.1-0.5ml of 1:1000 injections) given s/c or i/m. Single dose should not exceed 1 mg (1ml). For infants and children, the recommended dose of adrenaline is 0.01mg/kg (0.01ml/kg of 1:1000 injections). Single paediatric dose should not exceed 0.5mg (0.5ml).

The mainstay in the treatment of severe anaphylaxis is the prompt use of adrenaline, which can be lifesaving. It should be used at the first suspicion of anaphylaxis. As with the use of all vaccines the vaccines should remain under observation for not less than 30 minutes for possibility of occurrence of rapid allergic reactions. Antihistaminic should also be available in addition to supportive measures such as oxygen inhalation.

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give VaxiFlu™ – 4 should be based on careful consideration of the potential benefits and risks.

Syncope (fainting) can occur in association with administration of injectable vaccines, including VaxiFlu™ – 4. Syncope can be accompanied by transient neurological signs such as visual disturbance, paraesthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. If VaxiFlu™ – 4 is administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the immune response may be lower than in immunocompetent persons as with other intramuscular injections, VaxiFlu™ – 4 should be given with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.

Vaccination with VaxiFlu™ – 4 may not protect all susceptible individuals.

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 results. The transient false positive reactions could be due to the IgM response by the vaccine.

4.5 Interaction with other medicinal products and other forms of interaction

VaxiFlu™ – 4 should not be mixed with any other vaccine in the same syringe or vial. There are insufficient data to assess the concurrent administration of VaxiFlu™ – 4 with other vaccines. When concomitant administration of other vaccines is required, the vaccines should be administered at different injection sites.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to VaxiFlu™ – 4.

4.6 Special Population

There are no adequate and well-controlled studies in pregnant women. Data from worldwide use of influenza vaccine during pregnancy do not indicate any adverse foetal or maternal outcomes attributable to the vaccine. Inactivated influenza vaccines can be used in all stages of pregnancy and lactation.

4.7 Effects on ability to drive and use machines

No studies on the effect of VaxiFlu™ – 4 on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse reactions that have been observed during clinical trial with Inactivated Influenza Vaccine (Split Virion) I.P. (Tetravalent) include (irrespective of causal association): injection site pain, injection site redness, injection site swelling, headache, fever, cold, vertigo, nausea, body ache, myalgia, fatigue and vomiting.

4.9 Overdose

Overdosage is unlikely to have any untoward effect.

5. PHARMACOLOGICAL PROPERTIES

VaxiFlu™ – 4 provides active immunization against four influenza virus strains (two A subtypes and two B types) contained in the vaccine.

VaxiFlu™ – 4 induces humoral antibodies against the haemagglutinins. These antibodies neutralize influenza viruses. Specific levels of hemagglutination-inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HI antibody titers have been used as a measure of vaccine activity. In some human challenge studies, HI antibody titres of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects. Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual replacement of one or more influenza viruses in each year's influenza vaccine**.**

5.1 PHARMACODYNAMICPROPERTIES

Immune Response:

The immunogenicity of VaxiFlu™ – 4 has been evaluated in the clinical trials conducted in India.

Adult Subjects (≥18 years of age)

The immunogenicity and safety of VaxiFlu™ – 4 was evaluated and compared to Vaxigrip of M/s Sanofi Pasteur India Private Limited a randomized, single blind, multicentric phase II / III clinical trial in healthy adult subjects aged ≥18 years.

Among the 170 subjects analysed for immunogenicity in the VaxiFlu™ – 4 Group, proportion of subjects having seroconversion or a significant increase in anti-haemagglutinin antibody titres was 93.5% for A/H1N1, 90.0% for A/H3N2, 70.0% for B/Phuket and 82.9% for B/Brisbane.

These proportions were greater than the WHO recommended limit of 40% for all the four strains. The Geometric Mean of the fold rise in the anti-haemagglutinin antibody titres in the VaxiFlu-4 Group was 28.6 for A/H1N1, 19.4 for A/H3N2, 5.8 for B/Phuket and 8.1 for B/Brisbane strain. This was also more than the recommended fold rise of 2.5 for all the four strains. The proportion of subjects achieving a HI titre of more than 1:40 was also more than the WHO recommended proportion of 70% for all the four strains, the results being 98.2% for A/H1N1 and A/H3N2, 85.3% for B/Phuket and 97.7% for B/Brisbane. These results show that VaxiFlu™ – 4 fulfils all the three serologic parameters set by both the CHMP (Committee for Medicinal Products for Human Use) and the WHO for all the four strains in the vaccine. Moreover, the vaccine also fulfils the criteria set by the Center for Biologics Evaluation and Research (CBER) for regulatory approval of a new seasonal inactivated influenza vaccine which requires the lower limits of the 95% CI of the seroconversion rate and the seroprotection rate to be above 40% and 70%, respectively.

Paediatric Subjects (6 months to 17 years of age)

The immunogenicity and safety of VaxiFlu™ – 4 was evaluated and compared to Vaxigrip of M/s Sanofi Pasteur India Private Limited (trivalent Influenza vaccine) in a randomized, single blind, multicentric phase III clinical trial in healthy children aged 6 months to 17 years. The enrolled subjects of 9 to 17 years were administered 0.5 ml single dose of allocated study vaccine while the enrolled subjects of 3 to 8 years age group were administered 2 doses of the allocated study vaccine (0.5 ml per dose) with an interval of 28 days between two doses in the study. The subjects of 6 to 35 months were also administered 2 doses of allocated study vaccine at an interval of 4 weeks but the volume per dose administered was half than that administered to the subjects of 3 to 8 years age group. The seroconversion rate 28 days after vaccination with VaxiFlu-4 was 90.0% for A/H1N1, 94.0% for A/H3N2, 88.0% for B/Brisbane and 88.0% for B/Phuket in the subjects of 9 to 17 years and it was 93.8% for A/H1N1, 89.6% for A/H3N2, 89.6% for B/Brisbane and 83.3% for B/Phuket in the subjects of 3 to 8 years. The Seroprotection rate 28 days after vaccination with VaxiFlu™ – 4 was 100.0% for A/H1N1, 100.0% for A/H3N2, 92.0% for B/Brisbane and 88.0% for B/Phuket in the subjects of 9 to 17 years and it was 100.0% for A/H1N1, 100.0% for A/H3N2, 91.7%% for B/Brisbane and 87.5% for B/Phuket in the subjects of 3 to 8 years. The GMT of HI antibodies were 1245.0 for A/H1N1, 2137.8 for A/H3N2, 232.6 for B/Brisbane and 117.9 for B/Phuket in the subjects of 9 to 17 years and it was for 854.3

A/H1N1, 2031.9 for A/H3N2, 169.5 for B/Brisbane and 88.5 for B/Phuket in the subjects of 3 to 8 years. The immunogenicity of VaxiFlu™ – 4 was comparable to the comparator trivalent Influenza vaccine for 3 strains contained in it (A/H1N1, A/H3N2 and B/Brisbane) while it was better than the comparator vaccine for additional B strain (B/Phuket) which was not available in the comparator vaccine.

Paediatric Subjects (6 months to 3 years of age)

The immunogenicity and safety of VaxiFlu™ – 4 was evaluated and compared to Fluarix-Tetra of M/s GlaxoSmithKline Pharmaceuticals Limited in a randomized, single blind, multicentric phase III clinical trial in healthy children aged 6 months to 3 years. The enrolled subjects were administered 2 doses of the allocated study vaccine (0.5 ml per dose) with an interval of 28 days between two doses during the study. The seroprotection rate, 28 days after last vaccination with VaxiFlu™ – 4 was 100.0% for A/H1N1, 95.3% for A/H3N2, 99.4% for both B/Victoria and B/Yamagata strains. The seroconversion rate, 28 days after last vaccination with VaxiFlu™ – 4 was 100.0% for A/H1N1, 90.1% for A/H3N2, 97.7% for both B/Victoria and B/Yamagata strains. The GMTs of HI antibodies 28 days after last vaccination with VaxiFlu™ – 4 were 905.1 for A/H1N1, 96.7 for A/H3N2, 230.0 for B/Victoria and 217.3 for B/Yamagata strain. VaxiFlu-4 was found to be non-inferior to Fluarix-Tetra for the seroprotection rate, seroconversion rate and GMTs of antibodies for all the above 4 strains.

5.2 PHARMACOKINETIC PROPERTIES

Evaluation of pharmacokinetic properties is not required for vaccines

5.3 Preclinical safety data

5.3.1 Animal Toxicology & Pharmacology:

Non-clinical data reveal no special hazard for humans based on conventional single-dose and repeated-dose toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Phosphate Buffer Saline

6.2 Incompatibilities

- This vaccine must not be mixed with other medicinal products.

6.3 Shelf life

- The expiry date of the vaccine is indicated on the label and carton of the product.

6.4 Special precautions for storage

The Vaccine should be stored at a temperature between 2 to 8°C. Transportation should also be at 2 to 8°C.

Storage Condition: Store at 2°C to 8°C. Do Not Freeze.
Discard Vaccine if Frozen.
Keep the syringe in the outer carton in order to protect from light
Keep out of reach of children.

6.5 Nature and contents of container

- 2R Clear tubular Glass Vial - USP Type I with 13 mm Grey Bromo Butyl Rubber Stopper and 13 mm Aluminium Flip Off Seals.

- Pre-Filled Syringe (PFS) device- USP Type I glass with Bromo Butyl plunger stopper.

6.6 Special precautions for disposal

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

7. Details of manufacturer

Zydus Lifesciences Limited
Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, 49 & 50,
Sarkhej- Bavla N.H. 8A, Opp. Ramdev Masala,
Village: Changodar, Taluka: Sanand,
Dist. Ahmedabad – 382 213, State: Gujarat, India.

8. MARKETING AUTHORISATION NUMBER(S)

Permission No. MF – 176/2016

9. DATE OF FIRST AUTHORISATION

Dated 01.11.2016, amendment dated: 10.12.2018; 24.05.2023, 13.10.2023 and 04.03.2024.

SmPC updated on: 09.07.2024