Summary of Product Characteristics for Pharmaceutical Products

1.Name of the Medicinal Product

Influenza Vaccine (Split Viron), Inactivated, Quadrivalent
Strength: 0.5ml/dose
Pharmaceutical form: Vial

2.Qualitative and Quantitative Composition

2.1 Qualitative declaration

This product is prepared by inoculating influenza A and B virus strains recommended by the World Health Organization (WHO) into eggs, followed by culturing, virus harvesting, concentrating, purifying, virus inactivation, splitting and post-splitting purifying. It is a slightly opalescent liquid.

Active ingredient: Hemagglutinin of flu strains used in the year. Each 0.5 mL of this product contains: A/Victoria/2570/2019 (H1N1) pdm09-like virus, A/Darwin/9/2021 (H3N2)-like virus, B/Australa/1359417/2021 (B/Victoria lineage)-like virus, B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Excipients: potassium dihydrogen phosphate, anhydrous disodium hydrogen phosphate, sodium chloride and potassium chloride.

2.2 Quantitative declaration

0.5 ml per vial

0.5 ml per single human dose, containing 15 μg of Hemagglutinin of each of the influenza virus strains and potassium dihydrogen phosphate, anhydrous disodium hydrogen phosphate, sodium chloride and potassium chloride.

3.Pharmaceutical Form

Injection in vial. with 0.5ml/ vial. It is a slightly opalescent liquid.

4.Clinical Particulars

4.1 Therapeutic indication

The vaccination with this product can stimulate the body to produce anti-influenza virus immunity; It is used to prevent influenza caused by corresponding influenza viruses.

4.2 Posology and method of administration

This product is used before or during the influenza season. For the population aged 3 and above, 1 single dose of 0.5mL is used. It should be injected intramuscularly into the lateral deltoid muscle of upper arm.

4.3 Contraindication

(1) Individuals who are known to be allergic to any of the ingredients contained in this product, including excipients, formaldehyde and Triton X-100.

(2) Individuals who are suffering from acute diseases, severe chronic diseases, acute exacerbation of chronic diseases, colds or fever.

(3) Individuals with uncontrolled epilepsy and other progressive nervous system disorders, and patients with a history of Guillain-Barre syndrome.

The individual with any of the above conditions is forbidden to use this product, and should let the doctor know the condition in time.

4.4 Special Warning and Precaution for use

(1). The following individuals should use the product with caution: those with family and individual history of convulsions, those suffering from chronic diseases, those with epilepsy history and those with allergic constitution.

(2). The product can't be used if the vaccine container has cracks, or the label is unclear, or the product expires, or the appearance of the vaccine is abnormal, such as the vaccine is turbid, or there are lumps or floccules that cannot be dispersed on shaking.

(3). The vaccine should be used immediately once the vial is opened. Do not allow the disinfectant to come into contact with the vaccine when opening the vial or injecting the vaccine..

(4).Freezing and split use are strictly prohibited.

(5). This product shall not be mixed with other medical products in a syringe and injected together.

(6). For individuals with thrombocytopenia or hemorrhagic disease, intramuscular injection of this product may cause bleeding.

(7). Intravenous injection is strictly prohibited.

(8).Adrenaline and other drugs should be provided for emergency use in case of occasional severe allergic reaction. Vaccinees should be observed on site for at least 30 minutes after injection.

(9). Individuals with any neurological reaction after injection are forbidden to use this product again.

(10). Individuals injected with immunoglobulin should be vaccinated with this product at least one month apart to avoid affecting the immune effect.

(11). Individuals with low immune function should consult a doctor before using this product.

(12) This product must be used in validity period.

4.5 Interaction with other medication products and other forms of interaction

N.A

4.6 Fertility, pregnancy and lactation

There are no clinical trial data on the use of this product in pregnant and lactating women. If this population needs to use this product, it is recommended to make a decision after benefit/risk assessment with doctors.

4.7 Effect on ability to drive and machine

N/A

4.8 Undesirable effects

a. Summary of the safety profile

According to the incidence of adverse reactions recommended by the Council for International Organizations of Medical Sciences (CIOMS), the following description is made.

Non-injection site (systemic adverse reactions)

Very common: fever;

Common: headache, fatigue;

Occasional: nausea and vomiting, diarrhea, muscle pain, cough, allergy.

Injection site (local adverse reactions)

Common: pain, swelling;

Occasional: redness, itching and callosity.

The following non-solicited adverse reactions of the population aged 60 and above in Phase III clinical trial of this product are also reported (the total incidence rate was 1.88%): conjunctivitis, rhinorrhea, nasal congestion, throat irritation, laryngeal edema, dizziness, tinnitus, local paralysis of one limb, muscle spasm, chest pain, axillary pain and pruritus.

b. Description of selected adverse reactions

Participants were monitored after each vaccination for 30 minutes for immediate reactions. Solicited injection site and systemic reactions were recorded in a diary card for 7 consecutive days after each vaccination. Participants were monitored for 28 days for unsolicited adverse events and for 12 months post-vaccination for visits to an emergency room, unexpected visits to an office physician, and serious adverse events. Unsolicited adverse event information was obtained either by telephone interview or at an interim clinic visit.

d. Pediatric population

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 PPB website https://pv.pharmacyboardkenya.org.

4.9 Overdose

Not yet clear.

5. Pharmacological properties

5.1 Pharmacodynamic properties

a. Pharmacotherapeutic group and ATC code:

N/A.

b. Mechanism of action

Through 1 dose of immunization, specific neutralizing antibodies of a certain concentration with protective effect can be produced in susceptible persons above 3 years old to prevent influenza caused by corresponding influenza viruses.

c. Pharmaco-dynamic effects.

Refer to item d. Clinical efficacy and safety.

d. Clinical efficacy and safety

(1) Efficacy test results

Two randomized, blind and controlled Phase III clinical trials for this product were finished in China.

a. Phase III clinical trial in population aged 3 ~ 60

In a randomized, double-blind, controlled Phase III clinical trial completed in China, a total of 2400 healthy subjects aged 3 ~ 60 were enrolled, among which 2394 subjects were randomly vaccinated with one dose of this product (test group) or one of the two trivalent seasonal influenza control vaccines (control group) according to the ratio of 1: 1: 1.

Blood samples of the subjects were collected before and 28 days after the immunization, and the titer of influenza virus HI antibody in serum of subjects was detected by micro hemagglutination inhibition test. The GMT of H1N1, H3N2, B (Y) and B (V) antibodies in the whole population of the test group were 575.54, 486.31, 236.42 and 64.07, respectively. After immunization, the GMT growth multiple (GMI) of antibody was 28.70, 13.00, 6.36 and 5.21 respectively (see Table 1 for details). The positive conversion rates of H1N1, H3N2, B(Y) and B(V) antibodies in the whole population in the test group after immunization were 92.78%, 85.32%, 73.42%, and

66.84%, respectively; After immunization, the antibody protection rates were 99.37%,

99.24%, 98.48% and 82.28%, respectively (see Table 2 for details). The analysis results show that the primary study hypothesis is valid, and the results of FAS and PPS are consistent.

Table 1. GMT and GMI analysis of post-immunization antibodies in population aged 3 ~ 60 (PPS)

Antibody type	Group	Number of tests	Antibody GMT (95% CI)	GMT ratio (95% CI)	Antibody GMI (95% CI)
H1N1	Test group	790	575.54 (531.75-622.93)		28.70 (25.96-31.73)
	Control group B (Y)	787	499.69 (458.91-544.08)	1.15 (1.03, 1.29)	25.90 (23.55-28.50)
	Control group B (V)	788	572.35 (522.56-626.89)	1.01 (0.89, 1.13)	29.62 (26.81-32.71)

H3N2	Test group	790	486.31 (446.88-529.21)			13.00 (11.77-14.35)
	Control group B (Y)	787	533.34 (494.65-575.05)	0.91	(0.81, 1.02)	12.94 (11.73-14.28)
	Control group B (V)	788	624.98 (576.54-677.49)	0.78	(0.69, 0.87)	15.35 (13.86-17.00)
B (Y)	Test group	790	236.42 (220.26-253.77)			6.36 (5.85-6.91)
	Control group B (Y)	787	244.19 (227.22-262.42)	0.97	(0.88, 1.07)	6.83 (6.26-7.44)
	Control group B (V)	788	100.73 (92.91-109.22)	2.35	(2.11, 2.61)	2.66 (2.49-2.84)
B (V)	Test group	790	64.07 (59.66-68.81)			5.21 (4.88-5.57)
	Control group B (Y)	787	24.28 (22.65-26.02)	2.64	(2.39, 2.92)	1.96 (1.86-2.07)
	Control group B (V)	788	53.99 (50.14-58.14)	1.19	(1.07, 1.32)	4.50 (4.20-4.83)

Note: B(Y) was determined by B/Massachusetts/02/2012 standard antigen (NIBSC No. 13/106, Yamagata line), control group B(Y) did not contain B(V) antigen.

B (V) was determined by B/Brisbane/60/08 standard antigen (NIBSC No. 13/234, Victoria strain). The control group B (V) did not contain B (Y) antigen.

If the lower limit of the 95% CI of the antibody GMT ratio (test group/control group) is not less than 0.67, the non-inferiority test will be valid.

Table 2. Analysis of antibody positive conversion rate and protection rate of population aged 3 ~ 60 after immunization (PPS)

Antibody type	Group	Number of tests	Antibody positive conversion rate% (95% CI)	Rate difference of positive conversion rate% (95% CI)	Antibody protection rate (≥ 1:40)% (95% CI)
H1N1	Test group	790	92.78 (90.75-94.49)		99.37 (98.53-99.79)
	Control group B (Y)	787	93.01 (91.00-94.69)	-0.23 (-2.76, 2.31)	96.95 (95.50-98.04)
	Control group B (V)	788	92.26 (90.17-94.03)	0.53 (-2.07, 3.12)	96.07 (94.46-97.31)
H3N2	Test group	790	85.32 (82.65-87.71)		99.24 (98.35-99.72)
	Control group B (Y)	787	83.99 (81.24-86.48)	1.33 (-2.23, 4.88)	99.75 (99.09-99.97)
	Control group B (V)	788	87.82 (85.33-90.02)	-2.50 (-5.86, 0.86)	99.49 (98.71-99.86)
Test group B (Y)		790	73.42 (70.19-76.47)		98.48 (97.36-99.21)

	Control group B (Y)	787	72.94 (69.69-76.01)	0.48 (-3.89, 4.86)	98.35 (97.19-99.12)	
	Control group B (V)	788	36.42 (33.05-39.89)	37.00 (32.44, 41.55)	88.07 (85.60-90.25)	
B (V)	Test group	790	66.84 (63.43-70.11)		82.28 (79.43-84.88)	
	Control group B (Y)	787	16.39 (13.87-19.17)	50.44 (46.26, 54.62)	42.19 (38.71-45.72)	
	Control group B (V)	788	56.35 (52.80-59.84)	10.49 (5.72, 15.26)	73.98 (70.77-77.02)	

Note: B(Y) was determined by B/Massachusetts/02/2012 standard antigen (NIBSC No. 13/106, Yamagata line), control group B(Y) did not contain B(V) antigen.

B (V) was determined by B/Brisbane/60/08 standard antigen (NIBSC No. 13/234, Victoria strain). The control group B (V) did not contain B (Y) antigen.

If HI antibody titer <1:10 before immunization, and HI antibody titer≥ 1:40 after immunization, it is positive conversion; Or before immunization, the titer of HI antibody was ≥ 1: 10, and after immunization, the titer of HI antibody increased 4 times, it is also positive conversion

If the rate difference of antibody positive conversion rate (test group minus control group) 95%CI lower limit> -10%, the non-inferiority test is valid.

HI antibody titer ≥ 1: 40 after immunization is regarded as having antibody protection.

b. Phase III clinical trials in population aged 60 and above

In a randomized, blind and controlled Phase III clinical trial completed in China, a total of 1920 healthy subjects aged 60 and above were enrolled, among which 1918 were randomly vaccinated with 1 dose of this product (test group) or tetravalent seasonal influenza control vaccine (control group) at the ratio of 1: 1.

Blood samples of the subjects were collected before and 28 days after immunization, and the titer of influenza virus HI antibody in the serum of the subjects was detected by the micro-hemagglutination inhibition test method. GMT of H1N1, H3N2, B (Y) and B (V) antibodies of the whole population in the test group were 452.48, 163.71, 245.53 and 172.81 respectively; After immunization, the GMT growth multiple (GMI) of antibody was 27.62, 14.48, 5.66 and 9.17 respectively (see Table 3 for details). After immunization, the positive conversion rates of H1N1, H3N2, B (Y) and B (V) antibodies in the whole population of the test group were 89.55%, 84.33%, 76.87% and 87.21%, respectively. The antibody protection rates after immunization were 95.20%, 93.28%, 99.47% and 96.70% (see Table 4 for details). The analysis results showed that the primary study hypothesis was valid, and the results of the FAS were consistent with those of the PPS.

Table 3. GMT and GMI analysis of post-immunization antibodies in population aged 60 years and above (PPS)

Antibody type	Group	Number of tests	Antibody GMT (95% CI)	GMT ratio (95% CI)	Antibody GMI (95% CI)
H1N1	Test group	938	452.48 (414.64, 493.77)	2.83 (2.50, 3.20)	27.62 (25.17, 30.32)
	Control group	946	159.91 (146.59, 174.43)		9.52 (8.65, 10.48)
H3N2	Test group	938	163.71 (152.39, 175.86)	1.80 (1.63, 1.99)	14.48 (13.32, 15.75)
	Control group	946	90.81 (84.56, 97.53)		7.48 (6.90, 8.11)
B (Y)	Test group	938	245.53 (232.99, 258.75)	1.06 (0.99, 1.14)	5.66 (5.31, 6.03)
	Control group	946	231.04 (219.29, 243.43)		4.93 (4.65, 5.22)
B (V)	Test group	938	172.81 (163.22, 182.97)	1.07 (0.99, 1.16)	9.17 (8.56, 9.82)
	Control group	946	161.15 (152.24, 170.58)		7.71 (7.26, 8.20)

Note: B (Y) was determined by B/Phuket/3073/2013 standard antigen (NIBSC No. 16/158, Yamagata strain).

B (V) was determined by B/Maryland/15/2016 (NYMC BX-69A) standard antigen (NIBSC number 18/104, Victoria strain).

If the 95% CI lower limit of antibody GMT ratio (test group/control group) is not lower than 0.67, the non-inferiority test is valid.

Table 4. Analysis of antibody positive conversion rate and protection rate of population aged 60 years and above (PPS)

Antibody type	Group	Number of tests	Antibody positive conversion rate % (95% CI)	Rate difference of positive conversion rate% (95% CI)	Antibody protection rate (≥ 1:40)% (95% CI)
H1N1	Test group	938	89.55 (87.42, 91.44)	21.58 (18.02, 25.15)	95.20 (93.63, 96.48)
	Control group	946	67.97 (64.89, 70.94)		78.33 (75.57, 80.92)
H3N2	Test group	938	84.33 (81.84, 86.60)	15.72 (11.95, 19.48)	93.28 (91.49, 94.80)
	Control group	946	68.60 (65.54, 71.55)		83.30 (80.77, 85.62)

B (Y)	Test group	938	76.87 (74.03, 79.53)	4.77 (0.84, 8.70)	99.47 (98.76, 99.83)	
	Control group	946	72.09 (69.12, 74.93)		99.26	(98.48, 99.70)
B (V)	Test group	938	87.21 (84.90, 89.28)	3.06 (-0.10, 6.24)	96.70	(95.34, 97.74)
	Control group	946	84.14 (81.66, 86.42)		97.36	(96.12, 98.28)

Note: B (Y) was determined by B/Phuket/3073/2013 standard antigen (NIBSC No. 16/158, Yamagata strain).

B (V) was determined by B/Maryland/15/2016 (NYMC BX-69A) standard antigen (NIBSC number 18/104, Victoria strain). If HI antibody titer <1:10 before immunization, and HI antibody titer≥ 1:40 after immunization, it is positive conversion; Or before immunization, the titer of HI antibody was ≥ 1: 10, and after immunization, the titer of HI antibody increased 4 times, it is also positive conversion

If the rate difference of antibody positive conversion rate (test group minus control group) 95%CI lower limit> -10%, the non-inferiority test is valid.

HI antibody titer ≥ 1: 40 after immunization is regarded as having antibody protection.

(2) Safety test results

1. Clinical trials of this product

Three clinical trials for this product were carried out in China. A total of 4360 subjects aged 3-60 years and above (2440 subjects aged 3-60 years and 1920 subjects aged 60 years and above) were enrolled, among which 1798 subjects were vaccinated with 1 dose of this product (839 subjects aged 3-60 years and 959 subjects aged 60 years and above). The systemic safety of the product was observed from the start of vaccination until 28 days after vaccination, and the serious adverse event was observed until 180 days after vaccination.

The solicited adverse reactions of population aged 3 and above in the clinical trial report of this product are described as follows:

Non-injection site (systemic adverse reactions)

Very common: fever;

Common: headache, fatigue;

Occasional: nausea and vomiting, diarrhea, muscle pain, cough, allergy.

Injection site (local adverse reactions)

Common: pain, swelling;

Occasional: redness, itching and callosity.

The following non-solicited adverse reactions of the population aged 60 and above in Phase III clinical trial of this product are also reported (the total incidence rate was 1.88%): conjunctivitis, rhinorrhea, nasal congestion, throat irritation, laryngeal edema, dizziness, tinnitus, local paralysis of one limb, muscle spasm, chest pain, axillary pain and pruritus.

2. Domestic and overseas clinical trials of similar products

In addition to the above adverse reactions, the following adverse reactions were observed in domestic and overseas clinical trials of similar products:

Non-injection site (systemic adverse reactions)

Very common: discomfort, joint pain, gastrointestinal symptoms, lethargy, irritability and loss of appetite;

Common: chills;

Occasional: vertigo, lymph node enlargement;

Rare: stomach pain, difficulty breathing, hyperhidrosis.

Injection site (local adverse reactions)

Common: ecchymosis;

Occasional: rash, hematoma, tenderness.

Serious adverse reactions

Rare: anaphylactoid purpura, systemic allergic reaction.

3. Post-marketing surveillance of similar products in overseas market

Additional safety data obtained from post-marketing surveillance of similar products overseas (generated by spontaneous reports from population of unknown size, for which the incidence of symptoms can't be estimated accurately and the correlation between symptoms and the use of vaccine can't be evaluated effectively) are summarized as follows:

Digestive system: abdominal pain or discomfort, swelling of the mouth, throat, and/or tongue;

Blood and lymphatic system: lymph node enlargement and thrombocytopenia;

Infection and invasive diseases: cellulitis, pharyngitis, rhinitis and tonsillitis at the injection site;

Nervous system: convulsion, encephalomyelitis, facial paralysis, Guillain-Barre syndrome, myelitis, neuritis, paresthesia, syncope;

Respiratory system: asthma, bronchospasm, difficulty breathing;

Cardiovascular system: tachycardia, vasculitis;

Dermatologic system: Angioedema, erythema, swelling, Stevens-Johnson syndrome, sweating, urticaria;

Eye: Eye pain/redness/swelling;

Immune system: anaphylactic shock, hypersensitivity, serum disease.

5.2 Pharmacokinetics properties

N/A

5.3 Preclinical safety data

No vaccine-related toxicity reaction has been found in the allergy test in guinea pig and the acute toxicity test in rat and the long-term toxicity test in rat and cynomolgus monkey and the reproductive toxicity test in rat.

6. Pharmaceutical particulars

6.1 List of excipients

No.	Excipient name
1	Potassium dihydrogen phosphate
2	Disodium hydrogen phosphate
3	Sodium chloride
4	Potassium chloride.

6.2 Incompatibilities

The Influenza Vaccine (Split Virion), Inactivated, Quadrivalent is an liquid injection, with a strength of 0.5mL/vial. Packaging materials that are in direct contact with the drug are important part of the drug and have a significant impact on stability of the drug quality. Due to the difference in raw materials and processes of packaging materials of different materials, the packaging materials may affect the quality of drugs by migration or adsorption with the ingredients of drug formulations. Influenza Vaccine (Split Virion), Inactivated, Quadrivalent in this study is an injection. Based on the route of administration, dosage form, and the possibility of interaction with packaging materials, the drug product has the highest risk and should be assessed for compatibility and safety between the drug product and container closure system. With reference to the Technical Guidelines for Compatibility Study of Chemical Drugs and Elastomeric Seals (Trial) and Technical Guidelines for Compatibility Study of Chemical Drug Injectables and Pharmaceutical Glass Packaging Containers (Trial) issued by the NMPA, the compatibility between Influenza Vaccine (Split Virion), Inactivated, Quadrivalent and container closure system (neutral borosilicate glass injection vial and rubber stoppers) was investigated. The study consists of extraction test, simulation tests, analytical methodological validation and migration tests, and assessment on the test results.

Wuhan Institute of Biology and Qingdao Sci-Tech have signed a package compatibility study service contract related to Influenza Vaccine (Split Virion), Inactivated, Quadrivalent. The package compatibility study protocol and preliminary test result report are shown in 3.2.P.2.4 - Appendix 1. The preliminary results of the compatibility study of packaging materials showed that the methodological validation met the

requirements, and no obvious erosion and peeling were found in each part of the simulated solution-treated vial; the test results of all organic compounds did not exceed AET (Analytical Evaluation Threshold = maximum daily human intake allowed /maximum daily dosage of drugs); there was no obvious erosion or peeling on the inner surface of the glass; the results of the elemental impurities test did not exceed 30% of the AET value, and the results met the requirements.

6.3 Shelf life

12 months.

6.4 Special precaution for storage

Store and ship at 2-8 ℃, and protect from light.

6.5 Nature and content of container

Packaging Material	**Container Material**
Injection vial made of neutral borosilicate glass tubing (2 mL)	Neutral borosilicate glass
Halobutyl rubber stopper for injection (13-A)	Halobutyl rubber
Caps made of aluminum-plastics combinations for antibiotic vials (13.3*6.1)	Aluminum-plastics

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7. Marketing authorization holder

Wuhan Institute of Biological Products Co., Ltd.
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Hubei Province, P.R.China
Post Code: 430207
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8. Marketing authorization number(s)

H2022/CTD9813/22647

9. Date of first authorization/renewal of the authorization

01-12-2022

10. Date of revision of the text

12/2024