SUMMARY OF PRODUCT CHARACTERISTICS

GSK Logo — **Influsplit Tetra *2020/2021***

1. NAME OF MEDICINAL PRODUCT

Influsplit Tetra *2020/2021*
Suspension for injection in a pre-filled syringe
Influenza split vaccine (inactivated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vaccine dose (0.5 ml) contains:
Active substances:
Influenza virus (inactivated, split antigens) of the following strains*:

A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09 – similar strain (A/Guangdong-Maonan/SWL1536/2019, CNIC-1909)	**15 micrograms HA****
A/Hong Kong/2671/2019 (H3N2) – similar strain (A/Hong Kong/2671/2019, NIB-121)	**15 micrograms HA****
B/Washington/02/2019 – similar strain (B/Washington/02/2019, wild type)	**15 micrograms HA****
B/Phuket/3073/2013 – similar strain (B/Phuket/3073/2013, wild type)	**15 micrograms HA****

* propagated in embryonated chicken eggs of healthy flocks of chickens
** haemagglutinin

This vaccine complies with the WHO (World Health Organisation) recommendations for the northern hemisphere and the EU decision for the **2020/2021** season.

Excipients with known effect

This vaccine contains approx. 3.75 mg of sodium chloride and approx. 1.3 mg of sodium monohydrogen phosphate x $12H_2O$ per dose (see Section 4.4).

This vaccine contains approx. 0.2 mg of potassium dihydrogen phosphate and approx. 0.1 mg of potassium chloride per dose (see Section 4.4).

Influsplit Tetra may contain traces of eggs (such as ovalbumin, chicken proteins), formaldehyde, gentamicin sulfate and sodium deoxycholate which are used in the manufacturing process (see Section 4.3).

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a pre-filled syringe.
The suspension is colourless to slightly opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Influsplit Tetra is indicated for the prevention of the genuine viral flu (influenza) in adults and children aged 6 months and over, caused by the two influenza A virus subtypes and the two influenza B lines contained in the vaccine (see Section 5.1).

The use of Influsplit Tetra should be based on the current STIKO recommendations (STIKO = Standing Committee on Vaccination at the Robert Koch Institute), which can be found on the Robert Koch Institute's website: www.rki.de.

An annual re-vaccination with the present vaccine is recommended as the immunity reduces in the year following the vaccination and circulating influenza virus strains may change from year to year.

4.2 Posology and method of administration

Dosage
Adults: 0.5 ml

Children:
Children aged 6 months and over: 0.5 ml

Children up to the age of 9 years who have never been vaccinated against influenza before should receive a second dose after a period of at least 4 weeks.

Children under the age of 6 months: The safety and efficacy of Influsplit Tetra in children under the age of 6 months has not been proven.

Method of administration

The vaccine is administered intramuscularly.

Necessary precautions in preparation for the vaccination shall be taken.

For information relevant to the handling of the vaccine before its application, see Section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in Section 6.1 or to other excipients in trace levels from egg (ovalbumin, chicken protein), formaldehyde, gentamicin sulfate, and sodium deoxycholate.

In case of febrile diseases and acute infections, the vaccination should be postponed until a later date.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name of the medicinal product and the batch number of the administered product must be clearly recorded.

It is part of good clinical practice to check the medical history (particularly with regard to previous vaccinations and the occurrence of undesirable effects) before vaccinating and to carry out a clinical examination.

As with all injectable vaccines, the appropriate means of medical treatment and monitoring should always be promptly available in the rare case of an anaphylactic reaction after administering the vaccine (adrenaline, corticosteroids, antihistamines).

The success of the vaccination may be restricted in patients suffering from an endogenous or iatrogenic immunosuppression.

Influsplit Tetra does not protect against all kinds of influenza virus strains. Influsplit Tetra shall provide protection against the strains contained in the vaccine and variants similar to these strains.

As with all other vaccines as well, it may happen that not everyone vaccinated with Influsplit Tetra is completely protected.

Influsplit Tetra may in no case be administered intravascularly.

As with other intramuscularly administered vaccines, Influsplit Tetra should be administered only cautiously to persons suffering from thrombocytopenia or a coagulation disorder as a haemorrhage may develop in these persons after intramuscular administration.

Particularly in adolescents, a syncope (faint) may occur as a psychogenic reaction to the needle injection after or even before a vaccination. During the recovery phase, it can be accompanied by various neurological symptoms such as temporary impaired vision, paraesthesia and tonic-clonic movements of the limbs. It is important to take measures in order to prevent injuries due to fainting.

For interferences with serological tests, see Section 4.5.

This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, i.e. it is almost "sodium-free"

This medicinal product contains less than 1 mmol of potassium (39 mg) per dose, i.e. it is almost "potassium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Influsplit Tetra may be administered to patients aged 50 years and over concomitantly with pneumococcal polysaccharide vaccines (see Section 5.1).

Influsplit Tetra may be administered concomitantly with the adjuvanted herpes zoster vaccine (Shingrix) (see Section 5.1).

In case of concomitant administration of another vaccine, different injection sites (contralateral) should be used.

The frequency of injection site soreness recorded with regard to patients concomitantly vaccinated with inactivated, tetravalent influenza vaccine (Influsplit Tetra) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) resembles that observed with PPV23 alone and is higher compared to Influsplit Tetra as sole vaccine.

The frequency of exhaustion, headaches, muscle pain and chills recorded with regard to patients concomitantly vaccinated with Influsplit Tetra and Shingrix resembles that observed with Shingrix alone and is higher compared to vaccination with Influsplit Tetra alone.

After the influenza vaccination, false-positive results of serological tests were observed that verified the presence of antibodies against HIV1, hepatitis C, and particularly HTLV1 by means of the ELISA method. The western blot technique refutes the false-positive ELISA test results. The temporary false-positive results could be due to the IgM immune response as a result of the vaccination.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inactivated influenza vaccines can be administered in all phases of pregnancy. Compared to the 1st trimester, more information is available on the safety of influenza vaccines during the 2nd and 3rd trimesters. In any case, the data after worldwide use of inactivated influenza vaccines do not suggest any harmful effects on the pregnant woman or the foetus.

Breast-feeding

Influsplit Tetra can be administered during lactation.

Fertility

No data on the effect on fertility are available.

4.7 Effects on the ability to drive and use machines

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

4.8 Undesirable effects

Clinical trials - Summary of the safety profile

In all age groups, the most common reported local adverse reaction after the vaccination was injection site soreness (15.6% to 40.9%).

In adults aged 18 and over, the most common reported general adverse reactions after the vaccination included exhaustion (11.1%), headaches (9.2%), and muscle pain (11.8%).

In persons aged 6 to 17 years, the most common reported general adverse reactions after the vaccination included exhaustion (12.6%), muscle pain (10.9%), and headaches (8.0%).

In persons aged 3 to 5 years, the most common reported general adverse reactions after the vaccination included drowsiness (9.8%) and irritability (11.3%).

In persons aged 6 months to 3 years, the most common reported general adverse reactions after the vaccination included irritability/agitation (14.9%), and lack of appetite (12.9%).

List of adverse reactions

The adverse reactions to Influsplit Tetra established in the different age groups are listed per vaccine dose in accordance with the following frequency classes:

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)

Adults

A clinical study on Influsplit Tetra conducted with adults investigated the frequency of adverse reactions in persons aged ≥18 years who were administered one dose of Influsplit Tetra (N = 3,036) or Influsplit SSW (trivalent influenza vaccine) (N = 1,010).
The following adverse reactions per vaccine dose were reported:
See table on the right top of the page.

System Organ Class	Frequency	Adverse reactions
Diseases of the nervous system	common	headaches
	uncommon	vertigo[1]
Gastrointestinal disorders	common	gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain)
Skin and subcutaneous tissue disorders	common	sweating[2]
Skeletal musculature, connective tissue and bone diseases	very common	muscle pain
	common	joint pain
General disorders and administration site conditions	very common	injection site soreness, exhaustion
	common	injection site redness, swollen injection site, chills, fever, lump at the injection site[2]
	uncommon	haematoma at the injection site[1], injection site itching[1]

[1]Reported as an undesirable effect
[2]Reported in previous Influsplit SSW studies

Children aged 6 months up to <18 years

Two clinical studies investigated the reactogenicity and the safety of Influsplit Tetra in children who had received either at least one dose of Influsplit Tetra or one dose of a control vaccine.

One study covered children aged 3 to < 18 years receiving Influsplit Tetra (N = 915) or Influsplit SSW (N = 912). The second study covered children aged 6 to < 36 months receiving Influsplit Tetra (N = 6,006) or a control vaccine (N = 6,012) (see Section 5.1).

The following adverse reactions per vaccine dose were reported:
See table on the top of page 3.

System Organ Class	Adverse reactions	Frequency		
		6 to <36 (months)	3 to <6 (years)	6 to <18 (years)
Metabolic and nutrition disorders	lack of appetite	very common	common	N/A
Psychiatric disorders	irritability/agitation	very common	very common	N/A
Diseases of the nervous system	drowsiness	very common	common	N/A
	headaches	N/A	N/A	common
Gastrointestinal disorders	gastrointestinal symptoms (including nausea, diarrhoea, vomiting, and/or abdominal pain)	N/A	N/A	common

Skin and subcutaneous tissue disorders	rash[1]	N/R	uncommon	uncommon
Skeletal musculature, connective tissue and bone diseases	muscle pain	N/A	N/A	very common
	joint pain	N/A	N/A	common
General disorders and administration site conditions	fever (≥38,0°C)	common	common	common
	fatigue	N/A	N/A	very common
	injection site soreness	very common	very common	very common
	injection site redness	very common	very common	very common
	swollen injection site	common	very common	very common
	chills	N/A	N/A	common
	injection site itching[1]	N/R	uncommon	uncommon
	lump at the injection site[2]	N/A	common	common

N/A=Not asked for in this age group
N/R=Not reported
[1]Reported as an undesirable effect
[2]Reported in previous Influsplit SSW studies

Data after initial marketing authorisation

The following adverse reactions were observed after the initial marketing of Influsplit SSW and/or Influsplit Tetra. Three of the influenza strains contained in Influsplit SSW are also included in Influsplit Tetra.

Refer to table in the middle of page 3.

System Organ Class	Frequency	Adverse reactions
Diseases of the blood and of the lymphatic system	rare	temporary lymphadenopathy
Disorders of the immune system	rare	allergic reactions (including anaphylactic reactions)
Diseases of the nervous system	rare	neuritis, acute disseminated encephalomyelitis, Guillain-Barré syndrome[1]
Skin and subcutaneous tissue disorders	rare	urticaria, itching, erythema, angioedema
General disorders and administration site conditions	rare	influenza-like illness, indisposition

[1] With regard to the Guillain-Barré syndrome, spontaneous reports have been received after the vaccination with Influsplit SSW and Influsplit Tetra; however, no causal relationship has been established between the vaccination and the Guillain-Barré syndrome.

Report of suspicion of adverse reactions

A report of any suspicion of adverse reactions after the initial marketing authorisation is of great importance. It facilitates a continuous monitoring of the risk-benefit balance of the medicinal product. Health-care professionals are requested to report any suspected case of adverse reaction to Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Institut, Paul-Ehrlich-Strasse 51-59, 63225 Langen, telephone: +49 6 10 37 70, facsimile: +49 61 03 77 12 34, website: www.pei.de.

4.9 Overdose

An overdose is not likely to produce an undesirable effect.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: influenza vaccine

ATC code: J07BB02

Mechanism of action

Influsplit Tetra provides active vaccination against four influenza virus strains (two A subtypes and two B lines) contained in the vaccine.
Influsplit Tetra induces humoral antibodies against haemagglutinins. These antibodies neutralise the influenza viruses.

Specific values of haemagglutination inhibition (HI) antibody titres after vaccination with inactivated influenza virus vaccines could not be correlated with the protection against the influenza disease, but the HI antibody titres have been used as a measure of vaccination activity. In some stress tests (challenge tests) with humans, HI antibody titres of ≥1:40 were associated with the protection against influenza diseases in up to 50 % of those persons.

Pharmacodynamic effects

Efficacy in children aged 6 to 35 months:
The efficacy of Influsplit Tetra was ascertained within the clinical study D-QIV-004, a randomised, observer-blinded, non-influenza vaccine comparator-controlled study carried out during the influenza seasons of the years 2011 to 2014. Healthy subjects aged 6 to 35 months (1:1) were randomised and received either Influsplit Tetra (N = 6,006) or a control vaccine (N = 6,012). They were administered either one dose (in the case of a previous influenza vaccination) or 2 doses at an interval of approx. 28 days each.

The efficacy of Influsplit Tetra was assessed on the basis of the seasonal influenza strain in order to prevent an influenza A and/or B disease confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) (moderate to severe progression of the disease and any severity). From 2 weeks after vaccination to the end of the flu season (approx. 6 months later), nasal swabs were taken after a flu-like illness and tested for influenza A and/or B by RT-PCR. In addition, all positive RT-PCR samples were tested for viability in cell cultures, and it was determined whether the virus strains were consistent with those in the vaccine.

Influsplit Tetra has met the primary and secondary efficacy criteria as shown in Table 1 on page 4.

Table 1: Influsplit Tetra: Morbidity and efficacy of the vaccine in children aged 6 to 35 months (according to protocol) ATP efficacy cohort – time-to-event analysis)

	Influsplit Tetra			Active comparison vaccine[1]			Vaccine efficacy	
	N[2]	n[3]	Morbidity (n/N) (%)	N[2]	n[3]	Morbidity (n/N) (%)	%	CI
Influenza disease of any severity[6]								
RT-PCR confirmed	5,707	344	6.03	5,697	662	11.62	49.8	41.8; 56.8[4]
Culture-confirmed	5,707	303	5.31	5,697	602	10.57	51.2	44.1; 57.6[5]
Strains consistent with those in the culture-confirmed vaccine	5,707	88	1.54	5,697	216	3.79	60.1	49.1; 69.0[5]
Moderate to severe influenza[7]								
RT-PCR confirmed	5,707	90	1.58	5,697	242	4.25	63.2	51.8; 72.3[4]
Culture-confirmed	5,707	79	1.38	5,697	216	3.79	63.8	53.4; 72.2[5]
Strains consistent with those in the culture-confirmed vaccine	5,707	20	0.35	5,697	88	1.54	77.6	64.3; 86.6[5]
Lower respiratory tract infection, RT-PCR confirmed	5,707	28	0.49	5,697	61	1.07	54.0	28.9; 71.0[5]
Acute otitis media, RT-PCR confirmed	5,707	12	0.21	5,697	28	0.49	56.6	16.7; 78.8[5]

CI: Confidence interval

[1]The children were administered an age-appropriate control vaccine without flu protection.

[2]Number of subjects that belonged to the ATP efficacy cohort – time-to-event analysis. This cohort included subjects who had met all eligibility criteria, were observed to determine efficacy, and complied with the study protocol until the onset of the disease.

[3]Number of subjects who reported at least one case of illness during the reporting period

[4]Two-sided confidence interval, 97.5%

[5]Two-sided confidence interval, 95%

[6]Influenza disease of any severity was defined as the occurrence of an influenza-like illness (ILI, e.g., fever ≥38°C and the following symptoms: cough, runny nose, nasal congestion or difficulties of breathing) or a consequence of a viral flu infection [acute otitis media (AOM) or a lower respiratory tract infection (LRI)].

[7]The moderate to severe influenza formed a subgroup of all cases of influenza with the following symptoms: fever >39°C, medically diagnosed AOM, medically diagnosed lower respiratory tract infection, medically diagnosed severe extrapulmonary complications, hospitalisation in the intensive care unit or supply of additional oxygen for more than 8 hours.

Exploratory analyses were performed on the vaccinated total cohort of 12,018 subjects (N = 6,006 for Influsplit Tetra, N = 6,012 for control). Influsplit Tetra was found to be effective in the prevention of moderate to severe influenza illnesses caused by the 4 strains (Table 2 on page 4), although there was a significant antigenic incongruence in 2 of the vaccine strains (A/H3N2 and B/Victoria).

Table 2: Influsplit Tetra: Morbidity rates and efficacy of the vaccine with RT-PCR confirmed moderate to severe influenza illnesses of subtype A and influenza line B in children aged 6 to 35 months (total vaccinated cohort)

	Influsplit Tetra			Active comparison vaccine[1]			Vaccine efficacy	
Strain	**N[2]**	**n[3]**	**Morbidity (n/N) (%)**	**N[2]**	**n[3]**	**Morbidity (n/N) (%)**	**%**	**95% CI**
A								
H1N1[4]	6,006	13	0.22	6,012	46	0.77	72.1	49.9; 85.5
H3N2[5]	6,006	53	0.88	6,012	112	1.86	52.7	34.8; 66.1
B								
Victoria[6]	6,006	3	0.05	6,012	15	0.25	80.1	39.7; 95.4
Yamagata[7]	6,006	22	0.37	6,012	73	1.21	70.1	52.7; 81.9

[1]Infants were administered an age-appropriate control vaccine without flu protection.
[2]Total number of subjects in the vaccinated total cohort
[3]Number of subjects who reported at least one case of illness during the reporting period
[4 to 7]The proportion of antigenically matched strains was 84.8%, 2.6%, 14.3% and 66.6% for A/H1N1, A/H3N2, B/Victoria and B/Yamagata, respectively.

In addition, in cases of RT-PCR confirmed cases of any severity, Influsplit Tetra reduced the risk of having to see a general practitioner by 47 % (relative risk (RR): 0.53 [95% CI: 0.46; 0.61], i.e. 310 to 583 consultations) and the risk of having to go to an emergency room by 79% (RR: 0.21 [95% CI: 0.09; 0.47], i.e. 7 to 33 consultations). The use of antibiotics was reduced by 50% (RR: 0.50 [95% CI: 0.42; 0.60], i.e. 172 to 341 subjects).

Efficacy in adults aged 18 to 64 years

In a clinical study involving more than 7,600 subjects in the Czech Republic and Finland, the efficacy of Influsplit SSW was assessed to avoid culture-confirmed influenza A and/or B cases in antigenically matched influenza virus strains.

The subjects were monitored for flu-like illnesses confirmed by culture (see results in Table 3 on page 5). The flu-like illness has been defined as at least one common symptom (fever >37.8°C and/or muscle pain) and at least one symptom of the respiratory tract (cough and/or sore throat).

Table 3: Morbidity rate and efficacy of the vaccine against the disease associated with evidence of an influenza A or B infection in adults aged 18 to 64 years (total vaccinated cohort)

			Morbidity (n/N)[1]	Efficacy (95% CI[2])		
	N	**n**	**%**	**%**	**LL[3]**	**UL**
Antigenically consistent, culture-confirmed influenza[4]						
Influsplit SSW	5,103	49	1.0	66.9	51.9	77.4
Placebo	2,549	74	2.9	-	-	-
All culture-confirmed influenza cases (consistent, mismatched and untyped)[5]						
Influsplit SSW	5,103	63	1.2	61.6	46.0	72.8
Placebo	2,549	82	3.2	-	-	-

[1] n/N: Number of cases/total number of subjects
[2] CI: Confidence interval
[3] LL: Lower limit

[4] There were no vaccine-matched, culture-confirmed cases of influenza strains A/New Caledonia/20/1999 (H1N1) or B/Malaysia/2506/2004 in the Influsplit SSW or placebo group.
[5] Of the 22 additional cases, 18 were mismatching and 4 were untyped; 15 of the 22 cases were A (H3N2) (11 cases with Influsplit SSW and 4 cases with placebo).

Immunogenicity was also evaluated in this study.

See table 4 on page 5.

Table 4: Postvaccinal GMT and seroconversion rates

Adults aged 18 to 64 years	Influsplit SSW[1] N=291
	GMT (95% CI)
A/H1N1	541.0 (451.0; 649.0)
A/H3N2	133.2 (114.6; 154.7)
B (Victoria)	242.8 (210.7; 279.7)
	Seroconversion rate (95% CI)
A/H1N1	76.3% (71.0;81.1)
A/H3N2	73.9% (68.4;78.8)
B (Victoria)	85.2% (80.6;89.1)

[1] contains A/H1N1, A/H3N2 and B (Victoria line)

Postvaccinal seroprotection rates were 97.6% against A/H1N1, 86.9% against A/H3N2, and 96.2% against B (Victoria).

Immunogenicity in children and adults:

The immunogenicity of Influsplit Tetra was assessed in terms of the geometric mean HI antibody titre (GMT) on day 28 after the last dose (children) or on day 21 (adults) and in terms of the HI seroconversion rate (4-fold increase in reciprocal titre or change from an undetectable [< 10] to a reciprocal titre of ≥ 40).

In study D-QIV-004 (children aged 6 to 35 months), the evaluation was carried out within a subcohort of 1,332 children (753 in the Influsplit Tetra group and 579 in the control group). The results are shown in Table 5.

The effect of a 2-fold dose in study D-QIV-004 was assessed by evaluating the immune response after re-vaccination one year later with 1 dose of Influsplit Tetra in the D-QIV-009 study. This study showed that 7 days after vaccination, immune memory was induced in children aged 6 to 35 months for all four vaccine strains.

The immunogenic non-inferiority of Influsplit Tetra was evaluated compared to Influsplit SSW in children in the D-QIV-003 study (approximately 900 children aged 3 to <18 years per treatment group who received one or two doses of the respective vaccine) and in adults in the D-QIV-008 study (approximately 1,800 subjects aged 18 and over who received one dose of Influsplit Tetra and approximately 600 subjects who received one dose of Influsplit SSW). In both studies, Influsplit Tetra elicited an immune response against the three common strains that was not inferior to Influsplit SSW, as well as a superior immune response against the B strain additionally contained in Influsplit Tetra. The results are shown in Table 5.

Table 5: Influsplit Tetra: GMT and seroconversion rates (SCR) after vaccination in children (6 to 35 months, 3 to < 18 years) and adults aged 18 years and over (according to protocol cohort)

Children aged 6 to 35 months (D-QIV-004)				
	Influsplit Tetra		**Comparator[1]**	
	N=750-753	**N'=742-746**	**N=578-579**	**N'=566-568**
	GMT[2] (95% CI)	**Seroconversion rate[2] (95% CI)**	**GMT[2] (95% CI)**	**Seroconversion rate[2] (95% CI)**
A/H1N1	165.3 (148.6;183.8)	80.2% (77.2;83.0)	12.6 (11.1;14.3)	3.5% (2.2;5.4)
A/H3N2	132.1 (119.1; 146.5)	68.8% (65.3;72.1)	14.7 (12.9; 16.7)	4.2% (2.7;6.2)
B (Victoria)	92.6 (82.3; 104.1)	69.3% (65.8;72.6)	9.2 (8.4; 10.1)	0.9% (0.3;2.0)
B (Yamagata)	121.4 (110.1;133.8)	81.2% (78.2;84.0)	7.6 (7.0;8.3)	2.3% (1.2;3.9)
Children aged 3 to < 18 years (D-QIV-003)				
	Influsplit Tetra		Influsplit SSW[3]	
	N=791	**N'=790**	**N=818**	**N'=818**
	GMT (95% CI)	**Seroconversion rate (95% CI)**	**GMT (95% CI)**	**Seroconversion rate (95% CI)**
A/H1N1	386.2 (357.3;417.4)	91.4% (89.2;93.3)	433.2 (401.0;468.0)	89.9% (87.6;91.8)
A/H3N2	228.8 (215.0;243.4)	72.3% (69.0;75.4)	227.3 (213.3;242.3)	70.7% (67.4;73.8)
B (Victoria)	244.2 (227.5;262.1)	70.0% (66.7;73.2)	245.6 (229.2;263.2)	68.5% (65.2;71.6)
B (Yamagata)	569.6 (533.6;608.1)	72.5% (69.3;75.6)	224.7 (207.9;242.9)	37.0% (33.7;40.5)
Adults aged 18 years and over (D-QIV-008)				
	Influsplit Tetra		Influsplit SSW[3]	
	N=1,809	**N'=1,801**	**N=608**	**N'=605**
	GMT (95% CI)	**Seroconversion rate (95% CI)**	**GMT (95% CI)**	**Seroconversion rate (95% CI)**
A/H1N1	201.1 (188.1;215.1)	77.5% (75.5;79.4)	218.4 (194.2;245.6)	77.2% (73.6;80.5)
A/H3N2	314.7 (296.8;333.6)	71.5% (69.3;73.5)	298.2 (268.4;331.3)	65.8% (61.9;69.6)
B (Victoria)	404.6 (386.6;423.4)	58.1% (55.8;60.4)	393.8 (362.7;427.6)	55.4% (51.3;59.4)
B (Yamagata)	601.8 (573.3;631.6)	61.7% (59.5;64.0)	386.6 (351.5;425.3)	45.6% (41.6;49.7)

N = Number of subjects for whom results were available after vaccination (for GMT)
N '= Number of subjects for whom results were available before and after vaccination (for SCR)
[1]Control vaccine without flu protection
[2]Results of the subcohort on immunogenicity
[3]B (Yamagata) strain not contained in Influsplit SSW

Simultaneous administration of pneumococcal polysaccharide vaccines:

In the clinical study D-QIV-010 involving 356 adults ≥ 50 years of age at risk for complications from influenza or pneumococcal disease, these subjects received Influsplit Tetra and a 23-valent pneumococcal polysaccharide vaccine (PPSV23), either concomitantly or sequentially separated. In neither of the two treatment groups, the immune response was

worse for all four strains of the Influsplit Tetra vaccine and the six pneumococcal serotypes (1, 3, 4, 7F, 14, and 19A) in the PPSV23 vaccine tested in the pre-determined primary analysis. In a descriptive analysis of six other pneumococcal serotypes in the vaccine (5, 6B, 9V, 18C, 19F, and 23F), the immune response in both groups was comparable, with 91.7% to 100% and 90.7% to 100% of the subjects who had developed seroprotective antibody levels against those serotypes in the separate administration group and in the concomitant administration group, respectively.

Simultaneous administration of adjuvanted herpes zoster vaccine (Shingrix):

In the Zoster-004 clinical study, 828 adults aged ≥50 years were randomised and then received 2 doses of Shingrix at an interval of 2 months, with one dose of Influsplit Tetra, either together with the 1st dose (N=413) or not together (N=415). The antibody responses to either vaccine were similar, regardless of whether or not the vaccines were administered together. Also, with regard to the geometric means of the haemagglutination inhibition (HI) antibody titres for all four strains contained in Influsplit Tetra, the study showed non-inferiority between simultaneous and non-simultaneous administration.

5.2 Pharmacokinetic properties

Not applicable to vaccines.

5.3 Preclinical safety data

Non-clinical data do not suggest any specific risks for humans in conventional studies conducted with regard to acute toxicity, local tolerance, toxicity with repeated doses, and toxicity to reproduction and development.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Sodium chloride
Sodium monohydrogen phosphate x $12H_2O$
Potassium dihydrogen phosphate
Potassium chloride
Magnesium chloride x $6H_2O$
RRR-α-tocopherol hydrogen succinate
Polysorbate 80 (Tween 80)
Octoxinol 10 (Triton X-100)
Water for injection purposes

6.2 Incompatibilities

As there is no information available from compatibility studies, the vaccine must not be mixed with other medicinal products.

6.3 Shelf-life

1 year.

The expiry date of the vaccine is stated on the label and on the packaging.

6.4 Special precautions for storage

The vaccine shall be stored at 2°C to 8°C in a refrigerator and must not be frozen.

The vaccine shall be kept in the original packaging to be protected from light.

6.5 Nature and contents of container

0.5 ml suspension in a pre-filled syringe (glass type I) with a plunger (grey butyl rubber) and a cap (bromobutyl and synthetic polyisoprene type I rubber) without a needle – package sizes of 1 or 10.

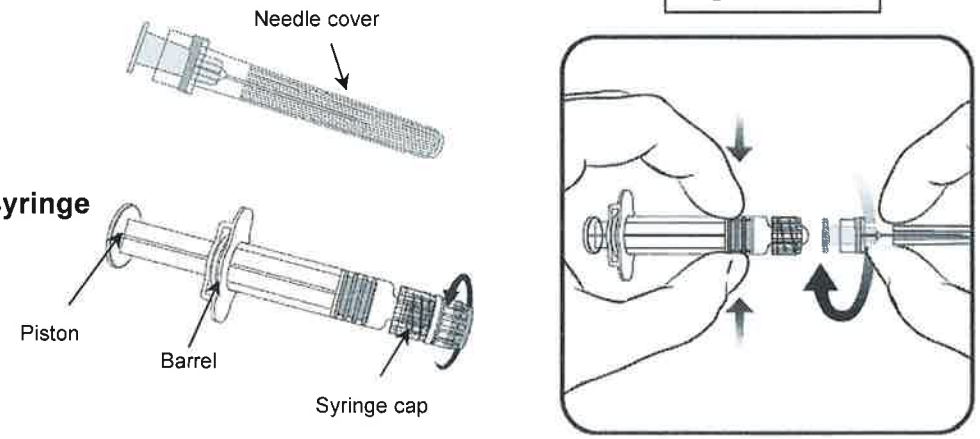
6.6 Special precautions for disposal and other handling of the product

The vaccine should be at room temperature when being administered. Before use, shake the syringe containing the vaccine. Before injecting the vaccine, check it visually.

Instructions on how to administer the vaccine in a pre-filled syringe without a needle

Follow the instructions in Figure 1 to attach the cannula/needle to the syringe.

Figure 1



1. Hold the syringe **barrel** in one hand (avoid holding the syringe by the piston) and unscrew the syringe cap by twisting it counterclockwise.
2. To attach the needle to the syringe, turn the needle clockwise into the syringe until it is properly seated (see Figure 1).
3. Remove the needle cover, which occasionally may stick a bit.
4. Administer the vaccine.

Unused medicinal product or waste material shall be disposed of in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

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Service Fax: 0800 1 22 33 66
E-Mail: produkt.info@gsk.com

8. MARKETING AUTHORISATION NUMBER(S)

PEI.H.11629.01.1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 March 2013 / 6 June 2017

10. DATE OF REVISION OF THE TEXT

April 2020

11. GENERAL CLASSIFICATION FOR SUPPLY

Subject to medical prescription

12. NOTES

According to Section 22 of the Protection against Infection Act, the vaccinator must enter all vaccinations in a vaccination card stating the date of vaccination, the trade name, the batch number, and the disease against which the patient was vaccinated.

Indicated vaccinations are often omitted because certain conditions are erroneously considered contraindications. For details please refer to the current STIKO recommendations (Standing Committee on Vaccination at the Robert Koch Institute, currently available at www.rki.de).

PAE 23173

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I, a sworn translator/interpreter for the English and French languages, publicly appointed by the President of the Supreme Regional Court of Dresden/Saxony, hereby certify the foregoing to be a correct and complete English translation of the German PDF document before me.

Radebeul, this **10 July 2020**

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