Date: 24 June 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

FLUENZ TETRA

International non-proprietary name: reassortant live attenuated influenza virus strains of types A/H1N1, A/H3N2, B/Yamagata and B/Victoria according to the annual WHO recommendation

Pharmaceutical form: suspension in a nasal spray

Dosage strength(s): $10^{7.0\pm0.5}$ FFU of each virus strain per 0.2 mL dose

Route(s) of administration: intranasal

Marketing Authorisation Holder: AstraZeneca AG

Marketing Authorisation No.: 68462

Decision and Decision date: approved on 11 May 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
FFU	Fluorescent focus units
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetic
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance reassortant live attenuated influenza virus strains of types A/H1N1, A/H3N2, B/Yamagata and B/Victoria of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Prophylaxis of influenza in children and adolescents from 24 months to 18 years of age.

2.2.2 Approved Indication

Active immunisation in children and adolescents from 24 months to 18 years of age. For prophylaxis of influenza caused by the two influenza A virus subtypes and the two influenza B virus subtypes contained in the vaccine.
The use of Fluenz Tetra should be based on official vaccination recommendations.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
0.2 mL (administered as 0.1 mL per nostril).
For children 2-8 years of age, who have not previously been vaccinated against seasonal influenza, a second dose should be given after an interval of at least 4 weeks.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	1 April 2021
Formal control completed	29 April 2021
List of Questions (LoQ)	25 August 2021
Answers to LoQ	22 November 2021
Predecision	18 February 2022
Answers to Predecision	24 March 2022
Final Decision	11 May 2022
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical Context

Influenza (flu) is a respiratory illness caused by influenza viruses. There are two main types of influenza that cause seasonal epidemics each year during the cold winter months: Type A and B.

Influenza is transmitted by direct or indirect contact with virus-containing respiratory secretions. Symptoms of influenza typically include fever, chills, cough, sore throat, muscle pain and runny nose. Elderly people, young children, pregnant women and people with certain health conditions are at higher risk of serious flu complications such as severe pneumonia and secondary bacterial infections.

In Switzerland, influenza results every year in approximately 112,000 to 275,000 doctor's consultations, several thousand hospitalisations due to complications and several hundred deaths (https://www.bag.admin.ch/bag/en/home/krankheiten/krankheiten-im-ueberblick/grippe.html).

The influenza vaccine is the most effective way of preventing flu and its complications. The seasonal influenza vaccine composition for the Northern hemisphere is recommended by the WHO in the first quarter of every calendar year based on the circulating viruses.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Quality Aspects

4.1 Drug Substance

The active substance consists of four different monovalent bulks of live attenuated influenza viruses (LAIV), with haemagglutinin (HA) and neuraminidase (NA) viral gene segments, from each of the specific four influenza virus strains that are recommended for the seasonal formulation every year by the WHO. The four strains used in the quadrivalent influenza vaccine consist of one influenza A (H1N1) virus strain, one influenza A (H3N2) virus strain, one influenza B (Yamagata lineage) virus strain and one influenza B (Victoria lineage) virus strain.

The LAIV monovalent bulk drug substance is prepared by the inoculation and growth of the Master Virus Seed (MVS) in embryonated Specific Pathogen Free (SPF) eggs. The MVS used in production consists in 6:2 reassortants containing a specific combination of six viral gene segments from an attenuated Master Donor Virus (MDV) and the two gene segments encoding haemagglutinin (HA) and neuraminidase (NA) antigens contributed by a wild-type (wt) influenza virus.

Virus particles from the pooled harvest fluid are clarified by filtration, and further concentrated and purified by tangential flow filtration and sucrose gradient flow ultracentrifugation. The concentrated virus particles are then diluted and sterile filtered before filling into bottles and storing at ≤ -60°C.

The manufacturing process has been validated with full-scale drug substance batches. The characterisation of the drug substance and its impurities was performed using state-of-the-art methods (e.g. SDS-PAGE, HA-content, total protein content, genomic consensus sequencing, as well as biological properties like attenuation, potency and immunogenicity).

The specifications for the pooled harvest fluid include bioburden and absence of adventitious agents tests; and those for the monovalent bulk include identity, potency and attenuation tests, as well as sterility and endotoxin tests.

Batch analysis data from commercial scale batches from the current manufacturing site were provided. Additional batch data from drug substance used in non-clinical studies and clinical trials were presented and their comparability was demonstrated. All the analytical methods are described and non-compendial methods have been validated in accordance with ICH guidelines. The drug substance is stored at ≤ -60°C. No significant changes are observed under the proposed storage conditions. A shelf life of 24 months has been accepted.

4.2 Drug Product

The quadrivalent live attenuated influenza vaccine (Q/LAIV) finished drug product is a blend of four strains of monovalent bulk drug substance, stabilised with concentrated gelatin-arginine-glutamate (cGAG) buffer and diluted to a final volume with sucrose phosphate (1X SP) buffer. One human dose consists of a 0.2 mL nasal sprayer capable of delivering 7.0 ± 0.5 log10 FFU of each strain, and 0.1 mL is sprayed into each nostril. The Q/LAIV drug product is presented as a clear to yellow slightly opalescent suspension that might contain little white particles, and it contains no preservatives.

The finished product manufacturing process includes blending of monobulk lots of the four strains and dilution with buffer and polysorbate to produce the quadrivalent bulk vaccine, aseptic filtration and filling. Process validation studies were conducted at commercial scale using three consecutive validation batches.

The specifications include appropriate tests for identity, potency on each individual strain, total potency, pH, endotoxin, ovalbumin, total protein, colour, opalescence and appearance, sterility and EDTA. All non-compendial methods are validated in accordance with ICH guidelines. Batch analysis results for the process validation batches and the clinical lot used for the pivotal studies comply with the release specification.

The container closure system in contact with the finished product consist of a single-dose type I glass nasal sprayer closed with a butyl rubber plunger stopper.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

The drug product is stored at 2-8°C. No significant changes are observed under the proposed storage conditions. A shelf life of 18 weeks has been accepted. The product should not be frozen and should be kept in the outer box in order to protect it from light.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated. The manufacturing process of the drug substance and drug product incorporate adequate control measures to prevent contamination and maintain control with regard to viral and non-viral contaminants.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Nonclinical Aspects

The Division Nonclinical Assessment conducted an abridged evaluation of the marketing authorisation application for Fluenz Tetra, which was based on the EMA assessment report (2010 (Fluenz) and 19.09.2013 (Fluenz Tetra)) provided by the applicant.

Overall, the submitted non-clinical documentation including answers to the List of Questions, is considered appropriate to support the approval of Fluenz Tetra for prophylaxis of influenza in children and adolescents from 24 months to 18 years of age.

The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the non-clinical studies that would be of concern for human use.

All non-clinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and corresponding product information from these authorities were used as a basis for the clinical and clinical pharmacology evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see the Appendix of this report.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Fluenz Tetra was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Fluenz Tetra

Composition

Active substances

Reassortant influenza virus strains* (live attenuated) of types** A/H1N1, A/H3N2, B/Yamagata and B/Victoria according to the annual WHO recommendation (for the Northern Hemisphere).
* propagated in fertilised hens' eggs from healthy chicken flocks.
** produced in VERO cells by reverse genetic technology. This product contains genetically modified organisms (GMOs).

Excipients

Saccharum, Dikalii phosphas, Kalii dihydrogenophosphas, Gelatina hydrolysata, Arginini hydrochloridum, Natrii hydrogenoglutamas monohydricus, Aqua ad iniectabile.

Fluenz Tetra may contain residues of eggs (e.g. ovalbumin, egg proteins) and Gentamicin sulphate, which are used in the manufacturing process (see "Contraindications").

Pharmaceutical form and active substance quantity per unit

Nasal spray, suspension in a single-use nasal applicator (0.2 ml). Each dose contains $10^{7.0\pm0.5}$ FFU (fluorescent focus units) of each of the four reassortant live attenuated influenza virus strains.
Colourless to pale yellow, clear to opalescent suspension; small white particles may be present.

Indications/Uses

Active immunisation in children and adolescents from 24 months to 18 years of age. For prophylaxis of influenza caused by the two influenza A virus subtypes and the two influenza B virus subtypes contained in the vaccine.
The use of Fluenz Tetra should be based on official vaccination recommendations.

Dosage/Administration

Usual dosage

0.2 ml (administered as 0.1 ml per nostril).
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each administered dose.

Children:

For children 2-8 years of age who have not previously been vaccinated against seasonal influenza, a second dose should be given after an interval of at least 4 weeks.

Mode of administration

Fluenz Tetra is intended for nasal administration only.
Do not inject Fluenz Tetra parenterally.
The dose of Fluenz Tetra is administered as a divided dose in both nostrils. After administering approximately half of the dose in one nostril, administer the other half of the dose in the other nostril immediately or shortly thereafter. The patient can breathe normally while the vaccine is being administered – there is no need to actively inhale or sniff.

For administration instructions, see section "Other instructions".

Contraindications

Hypersensitivity to the active substances, to any of the excipients (e.g., gelatine; see “Composition”), or to gentamicin (a possible trace residual).
Severe allergic reaction (e.g., anaphylaxis) to eggs or to egg proteins (e.g., ovalbumin).
Children and adolescents with clinical immunodeficiency due to conditions or immunosuppressive therapy, such as: acute and chronic leukaemias; lymphoma; symptomatic HIV infection; cellular immune deficiencies; and high-dose corticosteroids. Fluenz Tetra is not contraindicated for use in individuals with asymptomatic HIV infection, or in individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids, or in those receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency.

Children and adolescents younger than 18 years of age receiving salicylate therapy because of the association of Reye’s syndrome with salicylates and wild-type influenza infection.

Warnings and precautions

Risk in children <24 months of age

Do not administer Fluenz Tetra to children younger than 24 months. In a clinical study, an increase in hospitalizations was observed in children younger than 24 months after vaccination with the trivalent version of Fluenz, and an increased rate of wheezing was observed (see section “Undesirable Effects”).
These data with trivalent version of Fluenz are relevant to Fluenz Tetra because Fluenz Tetra is identical to the trivalent version of Fluenz with the only difference being the addition of a fourth strain (a second B strain).

Severe asthma or active wheezing

Fluenz Tetra should not be administered to children and adolescents with severe asthma or active wheezing because these individuals have not been adequately studied in clinical studies.

Management of acute allergic reactions

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

Vaccine recipients should be informed that Fluenz Tetra is an attenuated live virus vaccine and has the potential for transmission to immunocompromised contacts. Vaccine recipients should attempt to avoid, whenever possible, close association with severely immunocompromised individuals (e.g. bone marrow transplant recipients requiring isolation) for 1-2 weeks following vaccination. Peak vaccine virus recovery concentrations occurred 2-3 days post-vaccination in Fluenz clinical studies. In circumstances where contact with severely immunocompromised individuals is unavoidable, the potential risk of transmission of the influenza vaccine virus should be weighed against the risk of acquiring and transmitting wild-type influenza virus.
No data exist regarding the safety of intranasal administration of Fluenz Tetra in children with unrepaired craniofacial malformations.

Interactions

Children and adolescents under 18 years of age receiving salicylate therapy should avoid vaccination with Fluenz Tetra (see “Warnings and Precautions”). Do not use salicylates in children and adolescents younger than 18 years of age for 4 weeks after vaccination with Fluenz Tetra unless medically indicated.

The co-administration of trivalent Fluenz with the live attenuated vaccines against measles, mumps, rubella, varicella and orally-administered poliovirus has been studied. No clinically meaningful changes in immune responses to measles, mumps, varicella, orally-administered poliovirus or Fluenz have been observed. The immune response to rubella vaccine was significantly altered. However, this alteration might not be of clinical relevance with the two-dose immunisation schedule of the rubella vaccine. These studies with trivalent Fluenz are relevant to the use of Fluenz Tetra because Fluenz Tetra (influenza vaccine, live attenuated, nasal) is identical to Fluenz, with the only difference being the addition of a fourth strain (a second B strain).

The co-administration of Fluenz Tetra with inactivated vaccines has not been studied.

The concurrent use of Fluenz Tetra with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for influenza antiviral agents to reduce the effectiveness of Fluenz Tetra, it is recommended:

- not to administer Fluenz Tetra until 48 hours after the cessation of influenza antiviral therapy.
- not to administer influenza antiviral agents until two weeks after administration of Fluenz Tetra unless medically indicated.

If influenza antiviral agents and Fluenz Tetra are administered concomitantly, revaccination should be considered when appropriate.

Pregnancy, lactation

Pregnancy

There are to date only limited data from the use of Fluenz Tetra in pregnant women. There was no evidence of significant maternal adverse outcomes in 138 pregnant women who had a record of receiving trivalent version of Fluenz in a US based health insurance claims database. In more than 300 case reports in the AstraZeneca safety database and over 150 case reports from the US Vaccine Adverse Event Reporting System of the trivalent and quadrivalent version of Fluenz administration to pregnant women, no unusual patterns of pregnancy complications or foetal outcomes were observed.

While animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, and post-marketing data offer some reassurance in the event of inadvertent administration of the vaccine, Fluenz Tetra is not recommended during pregnancy.

Lactation

It is not known whether Fluenz Tetra is excreted in human milk. Therefore, Fluenz Tetra should not be used during breast-feeding.

Effects on ability to drive and use machines

The vaccine is not expected to have an effect on the ability to drive and use machines.

Undesirable effects

The safety experience with the trivalent version of Fluenz is relevant to the use of Fluenz Tetra because the trivalent version of Fluenz is identical to Fluenz Tetra with the only difference being the addition of a fourth strain (a second B strain) to Fluenz Tetra.
Safety data regarding use of Fluenz Tetra are based on data from Fluenz Tetra clinical studies in 2,231 children and adolescents 2 to 17 years of age, studies of the trivalent version of Fluenz in over 29,000 children and adolescents, and post-authorisation safety studies with the trivalent version of Fluenz in over 84,000 children and adolescents 2 to 17 years of age. Additional experience is available with marketed use of the trivalent version of Fluenz.
In clinical studies, the safety profile of Fluenz Tetra was similar to the safety profile of the trivalent version of Fluenz.
The most common adverse reaction observed in clinical studies was nasal congestion/rhinorrhoea.

List of adverse reactions

Frequency of occurrence of undesirable effects are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000).

Immune system disorders

Uncommon: Hypersensitivity reactions (including facial oedema, urticaria and very rare anaphylactic reactions)

Metabolism and nutrition disorders

Very common: Decreased appetite (18.3%)

Nervous system disorders

Common: Headache

Respiratory, thoracic and mediastinal disorders

Very common: Nasal congestion/rhinorrhoea (56.7%)
Uncommon: Epistaxis

Skin and subcutaneous tissue disorders

Uncommon: Rash

Musculoskeletal and connective tissue disorders

Common: Myalgia

General disorders and administration site conditions

Very common: Malaise (11.7%)
Common: Pyrexia

Description of specific adverse reactions and additional information

In an active-controlled clinical study (MI-CP111), an increased rate of hospitalizations (for any cause) up to 180 days after final vaccination dose was observed in children 6-11 months of age (6.1% trivalent version of Fluenz versus 2.6% injectable influenza vaccine). Most hospitalisations were due to gastrointestinal and respiratory tract infections and occurred more than 6 weeks post vaccination. The rate of hospitalizations was not increased in trivalent version of Fluenz recipients 12 months and older. In the same study, an increased rate of wheezing through 42 days was observed in children 6-23 months of age (5.9% trivalent version of Fluenz versus 3.8% injectable influenza vaccine). The rate of wheezing was not increased in trivalent version of Fluenz recipients 24 months of age and older. Fluenz Tetra is not indicated for use in children younger than 24 months (see section “warnings and precautions”).
Very rare reports of Guillain-Barré syndrome, exacerbation of symptoms of Leigh syndrome (mitochondrial encephalomyopathy), hypersensitivity reactions (including anaphylactic reactions, facial oedema and urticaria), epistaxis and rash have also been observed in the post-marketing setting with the trivalent version of Fluenz.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There have been occasional reports of administration of twice the recommended dose of Fluenz Tetra and the trivalent version of Fluenz in the post-marketing setting. The adverse reactions reported were similar to those seen with the use of the recommended single dose of Fluenz Tetra.

Properties/Effects

ATC code

J07BB03

Mechanism of action

Since 1985, two distinct lineages of influenza B viruses (Victoria and Yamagata) have circulated worldwide. Fluenz Tetra is a quadrivalent (also known as tetravalent) vaccine that contains antigens for four influenza virus strains, namely an A/(H1N1) strain, an A/(H3N2) strain, and two B strains (one from each lineage). The influenza virus strains in Fluenz Tetra are (a) *cold-adapted* (*ca*), (b) *temperature-sensitive* (*ts*), and (c) *attenuated* (*att*). As a result, the vaccine viruses only replicate in the nasopharynx and induce protective immunity.
No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of a possible 250 recovered isolates).

Immune mechanisms conferring protection against influenza following receipt of Fluenz Tetra vaccine are not yet fully understood. Likewise, naturally acquired immunity to wild-type influenza has not yet been completely elucidated. Serum antibodies, mucosal antibodies and influenza-specific T cells may play a role in prevention of infection and in recovery from infection.

Pharmacodynamics

The efficacy of Fluenz Tetra is based on data demonstrating laboratory-confirmed efficacy of the trivalent version of Fluenz in children and a comparison of post-vaccination geometric mean titers (GMTs) of hemagglutination inhibition (HAI) antibodies between individuals receiving the trivalent version of Fluenz and Fluenz Tetra. Clinical experience with the trivalent version of Fluenz is relevant to Fluenz Tetra because the trivalent version of Fluenz is identical to Fluenz Tetra with the only difference being the addition of a fourth strain (a second B strain) to Fluenz Tetra. The trivalent version of Fluenz has been administered to over 30,000 individuals in

controlled clinical studies over multiple years, in various regions and using different vaccine strains.

Clinical efficacy

Paediatric studies

Efficacy data in the paediatric population for the trivalent version of Fluenz originates from 9 controlled studies comprising over 20,000 children, conducted during 7 influenza seasons. Four placebo-controlled studies included second season revaccination. The trivalent version of Fluenz has demonstrated superiority in 3 active-controlled studies with injectable influenza vaccine. See Table 1 and Table 2 for a summary of efficacy results for the trivalent version of Fluenz in children.

Table 1: Efficacy of the trivalent version of Fluenz in placebo-controlled paediatric studies

Study Number	Region	Age Range[a]	Number of Study Participants[b]	Influenza Season	Efficacy (95% CI)[c] Matched strains	Efficacy (95% CI)[c] All strains regardless of match
D153-P502	Europe	6-35 M	1,616	2000-2001	85.4% (74.3, 92.2)	85.9% (76.3, 92.0)
				2001-2002	88.7% (82.0, 93.2)	85.8% (78.6, 90.9)
D153-P504	Africa, Latin America	6-35 M	1,886	2001	73.5% (63.6, 81.0)[d]	72.0% (61.9, 79.8)[d]
				2002	73.6% (33.3, 91.2)	46.6% (14.9, 67.2)
D153-P513	Asia/ Oceania	6-35 M	1,041	2002	62.2% (43.6, 75.2)	48.6% (28.8, 63.3)
D153-P522	Europe, Asia/ Oceania, Latin America	11-24 M	1,150	2002-2003	78.4% (50.9, 91.3)	63.8% (36.2, 79.8)
D153-P501	Asia/ Oceania	12-35 M	2,764	2000-2001	72.9% (62.8, 80.5)	70.1% (60.9, 77.3)
				2001-2002	84.3% (70.1, 92.4)[e]	64.2% (44.2, 77.3)[e]
AV006	USA	15-71 M	1,259	1996-1997	93.4% (87.5, 96.5)	93.4% (87.5, 96.5)
				1997-1998	100% (63.1, 100)	87.1% (77.7, 92.6)[f]

[a] M = months.

[b] Number of study participants for year 1 efficacy analysis.

[c] Reduction in culture-confirmed influenza illness relative to placebo.

[d] Data presented for clinical trial D153-P504 are for study participants who received two doses of study vaccine. In previously unvaccinated study participants, efficacy in Year 1 after one dose was 57.7% (95% CI: 44.7, 67.9) and 56.3% (95% CI: 43.1, 66.7), respectively, thus supporting the need for two doses of vaccine in previously unvaccinated children.

[e] In participants in study D153-P501 who received 2 doses in year 1 and placebo in year 2, efficacy in year 2 was 56.2% (95% CI: 30.5, 72.7) and 44.8% (95% CI: 18.2, 62.9), respectively, thus supporting the need for second-season revaccination.

[f] The primary circulating strain was antigenically dissimilar from the H3N2 strain represented in the vaccine; efficacy against the mismatched A/H3N2 strain was 85.9% (95% CI: 75.3, 91.9).

Table 2: Relative efficacy of the trivalent version of Fluenz in active-controlled paediatric studies with injectable influenza vaccine

Study Number	Region	Age Range[a]	Number of Study Participants[b]	Influenza Season	Improved Efficacy (95% CI)[c] Matched strains	Improved Efficacy (95% CI)[c] All strains regardless of match
MI-CP111	USA, Europe, Asia/ Oceania	6-59 M	7,852	2004-2005	44.5% (22.4, 60.6) fewer cases than with injectable	54.9% (45.4, 62.9)[d] fewer cases than with injectable
D153-P514	Europe	6-71 M	2,085	2002-2003	52.7% (21.6, 72.2) fewer cases than with injectable	52.4% (24.6, 70.5)[e] fewer cases than with injectable
D153-P515	Europe	6-17 Y	2,211	2002-2003	34.7% (3.9, 56.0) fewer cases than with injectable	31.9% (1.1, 53.5) fewer cases than with injectable

[a] M = months. Y = years. Age range as described in the protocol for the study.
[b] Number of study participants in the per-protocol population
[c] Reduction in culture-confirmed influenza illness relative to injectable influenza vaccine.
[d] Trivalent version of Fluenz demonstrated 55.7% (39.9, 67.6) fewer cases than injectable influenza vaccine in 3,686 children 6-23 months of age and 54.4% (41.8, 64.5) fewer cases in 4,166 children 24-59 months of age.
[e] Trivalent version of Fluenz demonstrated 64.4% (1.4, 88.8) fewer cases than injectable influenza vaccine in 476 children 6-23 months of age and 48.2% (12.7, 70.0) fewer cases in 1,609 children 24-71 months of age.

Study D153-P501: Paediatric Study

A randomized, double-blind, placebo-controlled trial (D153-P501) was performed in Asia for two consecutive seasons (2000-2001 and 2001-2002) to evaluate the efficacy of the trivalent version of Fluenz against culture-confirmed influenza illness in children 12-35 months of age without high-risk medical conditions. The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza. A total of 3,174 children were randomized 3:2 (vaccine: placebo) to receive 2 doses of study vaccine or placebo at least 28 days apart in Year 1. See Table 3 for a description of the results.
During the second year of Study D153-P501, for children who received two doses in Year 1 and one dose in Year 2, the trivalent version of Fluenz demonstrated 84.3% (95% CI: 70.1, 92.4) efficacy against culture-confirmed influenza illness due to antigenically matched wild-type influenza.

Study AV006: Paediatric Study

AV006 was a multi-centre, randomized, double-blind, placebo-controlled trial performed in U.S. children without high-risk medical conditions to evaluate the efficacy of the trivalent version of Fluenz against culture-confirmed influenza over two successive seasons (1996-1997 and 1997-1998). The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza in children who received two doses of vaccine in the first year and a single revaccination dose in the second year. During the first year of the study, 1,602 children 15-71 months of age were randomized 2:1 (vaccine: placebo). In Year 2, children remained in the same treatment group as in year one and received a single dose of the trivalent version of Fluenz or placebo. See Table 3 for a description of the results.

Table 3: Efficacy of the trivalent version of Fluenz vs. placebo against culture-confirmed influenza illness due to antigenically matched wild-type strains (studies D153-P501 and AV006, Year 1)

	D153-P501			AV006		
	Trivalent version of Fluenz n[b] (%)	**Placebo n[b] (%)**	**% Efficacy (95% CI)**	**Trivalent version of Fluenz n[b] (%)**	**Placebo n[b] (%)**	**% Efficacy (95% CI)**
	N[c] = 1,653	N[c] = 1,111		N[c] = 849	N[c] = 410	
Any strain	56 (3.4%)	139 (12.5%)	72.9%[d] (62.8, 80.5)	10 (1%)	73 (18%)	93.4% (87.5, 96.5)
A/H1N1	23 (1.4%)	81 (7.3%)	80.9% (69.4, 88.5)[e]	0	0	--
A/H3N2	4 (0.2%)	27 (2.4%)	90.0% (71.4, 97.5)	4 (0.5%)	48 (12%)	96.0% (89.4, 98.5)
B	29 (1.8%)	35 (3.2%)	44.3% (6.2, 67.2)	6 (0.7%)	31 (7%)	90.5% (78.0, 95.9)

[a] D153-P501 and AV006 data are for subjects who received two doses of study vaccine.
[b] Number and percent of subjects in per-protocol efficacy analysis population with culture-confirmed influenza illness.
[c] Number of subjects in per-protocol efficacy analysis population of each treatment group of each study for the "any strain" analysis.
[d] For D153-P501, influenza circulated through 12 months following vaccination.
[e] Estimate includes A/H1N1 and A/H1N2 strains. Both were considered antigenically similar to the vaccine.

During the second year of Study AV006, the primary circulating strain was the A/Sydney/05/97 H3N2 strain, which was antigenically dissimilar from the H3N2 strain represented in the vaccine,

A/Wuhan/359/95; the trivalent version of Fluenz demonstrated 87.0% (95% CI: 77.0, 92.6) efficacy against culture-confirmed influenza illness.

Study MI-CP111: Paediatric Comparative Study

A multinational, randomized, double-blind, active-controlled trial (MI-CP111) was performed to assess the efficacy and safety of the trivalent version of Fluenz compared to an injectable influenza vaccine made by Sanofi Pasteur Inc. (active control) in children <5 years of age. During the 2004-2005 influenza season, a total number of 3,916 children <5 years of age and without severe asthma, without use of bronchodilator or steroids and without wheezing within the prior 6 weeks were randomized to the trivalent version of Fluenz, and 3,936 were randomized to active control. Participants were then followed through the influenza season to identify illness caused by influenza virus. As the primary endpoint, culture-confirmed modified CDC-ILI (CDC-defined influenza-like illness) was defined as a positive culture for a wild-type influenza virus associated within ±7 days of modified CDC-ILI. Modified CDC-ILI was defined as fever (temperature ≥100°F (corresponding to approx. 37.8°C) oral or equivalent) plus cough, sore throat or runny nose/nasal congestion on the same or consecutive days.
In the primary efficacy analysis, the trivalent version of Fluenz demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control, as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 4 for a description of the results by strain and antigenic similarity.

Table 4: Comparative efficacy against culture-confirmed modified CDC-ILIa caused by wild-type strains in children <5 years of age

	Trivalent version of Fluenz			Active Control[b]			% Reduction in Rate for Trivalent version of Fluenz [c]	95% CI
	N	# of Cases	Rate (cases/N)	N	# of Cases	Rate (cases/N)		
Matched Strains								
All strains	3,916	53	1.4%	3,936	93	2.4%	44.5%	22.4, 60.6
A/H1N1	3,916	3	0.1%	3,936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3,916	0	0.0%	3,936	0	0.0%	--	--
B	3,916	50	1.3%	3,936	67	1.7%	27.3%	-4.8, 49.9
Mismatched Strains								
All strains	3,916	102	2.6%	3,936	245	6.2%	58.2%	47.4, 67.0
A/H1N1	3,916	0	0.0%	3,936	0	0.0%	--	--
A/H3N2	3,916	37	0.9%	3,936	178	4.5%	79.2%	70.6, 85.7
B	3,916	66	1.7%	3,936	71	1.8%	6.3%	-31.6, 33.3
Regardless of Match								
All strains	3,916	153	3.9%	3,936	338	8.6%	54.9%	45.4, 62.9
A/H1N1	3,916	3	0.1%	3,936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3,916	37	0.9%	3,936	178	4.5%	79.2%	70.6, 85.7
B	3,916	115	2.9%	3,936	136	3.5%	16.1%	-7.7, 34.7

ATP Population.

[a] Modified CDC-ILI was defined as fever (temperature ≥100°F oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.

[b] Injectable influenza vaccine made by Sanofi Pasteur Inc.

[c] Reduction in rate was adjusted for country, age, prior influenza vaccination status and wheezing history status.

Immunogenicity of Fluenz Tetra in Children and Adolescents

A multicentre, randomized, double-blind, active-controlled, non-inferiority study (MI-CP208) was performed to assess the immunogenicity of Fluenz Tetra compared to Fluenz (active control) in children and adolescents 2 through 17 years of age. A total of 2,312 children and adolescents were randomized at a 3:1:1 ratio to receive either Fluenz Tetra or one of two Fluenz comparator vaccines of the trivalent version of Fluenz, each containing a B strain that corresponded to one of the two B strains in Fluenz Tetra.

Immunogenicity was evaluated by comparing the 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dosing. Fluenz Tetra demonstrated immunologic non-inferiority to the two trivalent formulations of Fluenz, as the upper bound for each of the four 95% CIs for the post dose strain specific GMT HAI antibody ratios was less than the pre-specified non-inferiority criterion of ≤1.5. These data provide evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

Studies in Immunocompromised Individuals

Safety and shedding of vaccine virus following administration of the trivalent version of Fluenz were evaluated in children in a randomized (1:1), cross-over, double-blind, placebo-controlled trial in 24 HIV-infected children [median CD4 cell count of 1,013 cells/mm^3] and 25 HIV-negative children 1-7 years of age, and in a randomized (1:1), open-label, inactivated influenza vaccine-controlled trial in 243 HIV-infected children and adolescents 5-17 years of age receiving stable anti-retroviral therapy. Frequency and duration of vaccine virus shedding in HIV-infected individuals were comparable to that seen in healthy individuals. No adverse effects on HIV viral load or CD4 counts were identified following administration of the trivalent version of Fluenz. In the 5-17 year-old age group, one inactivated influenza vaccine recipient and one trivalent version of Fluenz recipient experienced pneumonia within 28 days of vaccination (days 17 and 13, respectively). The effectiveness of the trivalent version of Fluenz in preventing influenza illness in HIV-infected individuals has not been evaluated.

Twenty mild to moderately immunocompromised children and adolescents 5-17 years of age (receiving chemotherapy and/or radiation therapy or who had received chemotherapy in the 12 weeks prior to study enrolment) were randomized 1:1 to receive the trivalent version of Fluenz or placebo. Frequency and duration of vaccine virus shedding in these immunocompromised children and adolescents were comparable to that seen in healthy children and adolescents. The effectiveness of the trivalent version of Fluenz in preventing influenza illness in immunocompromised individuals has not been evaluated.

Study with Concomitant Live Vaccines

In Study AV018, concomitant administration of the trivalent version of Fluenz and live vaccines against MMR (manufactured by Merck & Co., Inc) and varicella virus (manufactured by Merck & Co.) was studied in 1,245 subjects 12-15 months of age. Subjects were randomized in a 1:1:1 ratio to MMR, varicella vaccine and placebo (group 1); MMR, varicella vaccine and trivalent version of Fluenz (group 2); or trivalent version of Fluenz alone (group 3). Immune responses to MMR and varicella vaccines were evaluated 6 weeks post-vaccination, while the immune responses to trivalent version of Fluenz were evaluated 4 weeks after the second dose. Adverse reactions were similar to those seen in other clinical trials with the trivalent version of Fluenz (see section “Undesirable Effects”). No

evidence of interference with immune response to measles, mumps, rubella, varicella and the trivalent version of Fluenz vaccines was observed.
Study D153-P522 investigated the concomitant use of the trivalent version of Fluenz and live vaccines against MMR (manufactured by GlaxoSmithKline) in 1,233 subjects aged 11-24 months. The participants were randomized at a ratio of 2:1 to receive LAIV+MMR or placebo+MMR. Seroresponse to measles and mumps was comparable in both groups. Compared with placebo, response rates to rubella in LAIV+MMR recipients were statistically lower (83.9% versus 78.0%) at a threshold value of 15 IU/mL, and the pre-defined criteria for non-inferiority were not fulfilled. In a post-hoc analysis using an alternative, generally-accepted threshold value of 10 IU/mL, the criteria for non-inferiority were met (93.4% versus 89.8%).

Pharmacokinetics

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional non-clinical studies of repeated dose toxicity, reproduction and developmental toxicity, local tolerance and neurovirulence.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.
Before use, the vaccine may be taken out of the refrigerator once for a maximum period of 12 hours and stored at a temperature not above 25°C. If the vaccine has not been used by the end of these 12 hours, it should be discarded.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

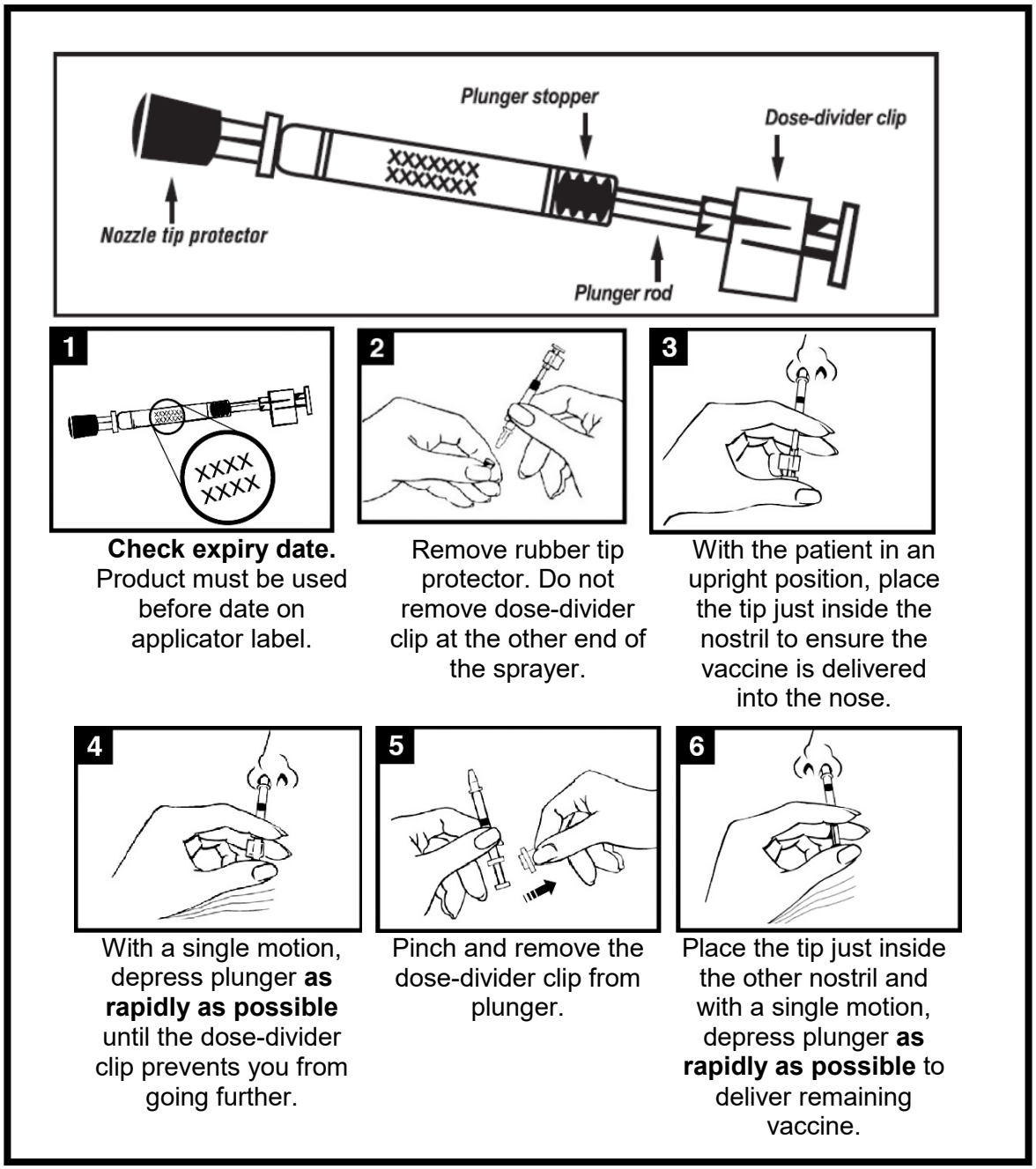
Fluenz Tetra **is for nasal use only.**

DO NOT INJECT. DO NOT USE A NEEDLE

- Do not use Fluenz Tetra if the expiry date has passed or the sprayer appears damaged, for example, if the plunger is loose or displaced from the sprayer, or if there are any signs of leakage.
- Check the appearance of the vaccine before administration. The suspension should be colourless to pale yellow, clear to opalescent. Small white particles may be present.
- Fluenz Tetra is administered as a divided dose in both nostrils.
- After administering half of the dose in one nostril, administer the other half of the dose in the other nostril immediately or shortly thereafter.
- The patient can breathe normally while the vaccine is being administered – there is no need to actively inhale or sniff.

Refer to the Fluenz Tetra administration diagram (Figure 1) for step-by-step administration instructions.

Figure 1:



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

Authorisation number

68462 (Swissmedic)

Packs

Packs with 1 or 10 nasal applicators (0.2 mL) [B]

Marketing authorisation holder

AstraZeneca AG, 6430 Baar

Date of revision of the text

February 2022