Date: 14 December 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Supemtek

International non-proprietary name: haemagglutininum influenzae A (H1N1) (rHA), haemagglutininum influenzae A (H3N2) (rHA), haemagglutininum influenzae B (rHA) (Yamagata lineage) and haemagglutininum influenzae B (rHA) (Victoria lineage)

Pharmaceutical form: solution for injection in pre-filled syringe

Dosage strength: 0.5 ml

Route(s) of administration: intramuscular

Marketing Authorisation Holder: Sanofi-Aventis (Suisse) SA

Marketing Authorisation No.: 68003

Decision and Decision date: approved on 28 October 2021

Note:

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

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- 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.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BC	Brighton Collaboration
CBER	Center for Biologics Evaluation and Research (US FDA)
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
e.g.	For example
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
GMT	Geometric Mean Titre
HA	Haemagglutinin
HAI	Haemagglutination inhibition
HI	Haemagglutination inhibition
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IIV4	Quadrivalent inactivated influenza vaccine
ILI	Influenza-like illness
INN	International Nonproprietary Name
LoQ	List of Questions
MAE	Medically-attended adverse event
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US FDA)
rHA	Recombinant haemagglutinin
RIV3	Trivalent recombinant influenza vaccine
RIV4	Quadrivalent recombinant influenza vaccine
RMP	Risk Management Plan
rtPCR	Reverse transcriptase polymerase chain reaction
rVE	Relative vaccine efficacy
SAE	Serious adverse event
SCR	Seroconversion rate
SMQ	Standardised MedDRA Queries
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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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 haemagglutininum influenzae A (H1N1) (rHA), haemagglutininum influenzae A (H3N2) (rHA), haemagglutininum influenzae B (rHA) (Yamagata lineage) and haemagglutininum influenzae B (rHA) (Victoria lineage) of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Supemtek is indicated for active immunisation for the prevention of influenza disease in adults 18 years of age and older.
Supemtek should be used in accordance with official recommendations.

2.2.2 Approved Indication

Supemtek is indicated for active immunisation in adults aged 18 years and over for prevention of influenza caused by the two influenza A virus subtypes and the two influenza B virus subtypes contained in the vaccine.
Supemtek should be used in accordance with official recommendations.

2.2.3 Requested Dosage

In adults 18 years of age and older: one dose of 0.5 ml

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	15 June 2020
Formal control completed	15 June 2020
List of Questions (LoQ)	8 October 2020
Answers to LoQ	4 January 2021
Preliminary decision	6 April 2021
Answers to preliminary decision	4 June 2021
Final Decision	28 October 2021
Decision	approval

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3 Medical Context

Influenza in humans can be caused by influenza type A and type B viruses and occurs in annual seasonal epidemics, predominantly during cold seasons of the Northern and Southern hemispheres. The burden of influenza morbidity and mortality is high with a greater burden attributable to influenza A, largely due to its greater virulence (A/H3N2 in particular).
Seasonal influenza causes 4 – 50 million symptomatic cases in EU/EEA each year, and 15,000 – 70,000 European citizens die every year of causes associated with influenza. Despite the often short duration of the illness, the yearly economic and healthcare burden of influenza is substantial. If these figures are extrapolated worldwide, the average global burden of seasonal influenza would be in the order of 600 million cases, being 3 million cases of severe illness and about 250,000 to 500,000 deaths per year.
In the 2019/2020 season both influenza types A and B co-circulated in Europe. Of the influenza A viruses, both influenza A(H1N1)pdm09 and A(H3N2) co-circulated. Of the circulating B viruses, the vast majority belonged to the B/Victoria lineage.[1]
In Switzerland each year influenza leads to 112,000 to 275,000 medical consultations (according to the Sentinella monitoring system). Due to its complications, influenza is responsible for thousands of hospitalisations and a few hundred fatalities each year.
Vaccination against influenza is the cornerstone public health intervention to reduce the annual burden of influenza epidemics.[2]
Annual/seasonal influenza vaccination is recommended by medical societies, vaccine advisory groups, and vaccination guidelines for people who are most at risk of developing serious complications from influenza. Older adults (in most countries defined as 65 years and above), people with chronic cardiac, respiratory, kidney, metabolic (e.g. diabetes) and immune system diseases, pregnant women and people in long-term care have a higher risk of severe influenza. Infants under the age of 6 months may also be at increased risk.
For the national recommendations, please refer to the respective Federal Office of Public Health (FOPH/BAG) website.[3]

A variety of influenza vaccines are available for the prevention of seasonal influenza disease, including a large number of inactivated vaccines produced by inactivating and purifying the influenza virus that has been grown in eggs or mammalian Madin-Darby Canine Kidney (MDCK) cells. Most of these products are split or subunit vaccines containing 15 µg of haemagglutinin (HA) per antigen and are available in either trivalent or quadrivalent formulations.
High-dose trivalent and quadrivalent inactivated products containing 60 µg of HA per antigen and an inactivated trivalent product containing 15 µg HA per antigen plus an adjuvant (MF59C.1, an oil-water emulsion) are typically indicated for the elderly population.

[1] https://flunewseurope.org/ (last accessed 07.06. 2020)
[2] https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/saisonale-grippe--lagebericht-schweiz.html (last accessed 07.06. 2020)
[3] https://www.bag.admin.ch/bag/en/home/krankheiten/krankheiten-im-ueberblick/grippe.html (last accessed 07.06. 2020)

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4 Quality Aspects

4.1 Drug Substance

The final product consists of four active substances, separately manufactured recombinant haemagglutinin (rHA) proteins, from each of the four influenza virus strains that are recommended for the seasonal formulation every year by the WHO and CHMP. The four strains 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 rHAs are expressed in proprietary *expres*SF+ insect cells (derived from *Spodoptera frugiperda* cells) using baculovirus (*Autographa californica* nuclear polyhedrosis virus) as the vector for protein expression. After harvest, the drug substance is purified by filtration and chromatography steps. The drug substance and its impurities were characterised using state of the art methods. The specifications include e.g. tests for appearance, identity, sterility, endotoxins, process-related impurities, rHA size, protein content and biological activity. Batch analysis data from commercial scale batches from the current manufacturing site were provided and indicate a consistent manufacturing process. The analytical methods are described and non-compendial methods have been validated in accordance with ICH guidelines. The drug substance is stored at 2- 8°C. No significant changes are observed within the proposed storage conditions. A shelf life of 12 months has been accepted.

4.2 Drug Product

The finished product is presented as a clear, colourless liquid supplied in a pre-filled syringe ready for use. One human dose consists of 0.5 mL solution. The formulation is prepared to contain the minimum dose of 45 µg rHA from each of the four virus strains in phosphate buffered saline without preservatives, antibiotics, or adjuvants. 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, sterile filtration, and filling. Process validation studies were conducted at commercial scale using three consecutive validation batches. The specifications include appropriate tests for appearance, identity, endotoxin, sterility, potency, total protein content, content uniformity, purity, total DNA, osmolality, pH, fill volume, and Triton X 100. 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 consists of a single dose type I glass syringe closed with a latex-free rubber plunger stopper. The drug product is stored at 2-8°C. No significant changes are observed within the proposed storage conditions. A shelf life of 12 months has been accepted. The product should not be frozen and should be kept in the outer carton in order to protect it from light.

4.3 Quality Conclusions

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

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Supemtek, a quadrivalent influenza vaccine containing recombinantly expressed haemagglutinin, the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the publicly available EMA assessment report of 17.09.2020.
Overall, the submitted nonclinical documentation is considered to be appropriate to support the approval of Supemtek in the proposed indication. The pharmaco-toxicological profile of the trivalent influenza vaccine containing haemagglutinin of two A strains and one B strain has been sufficiently characterised. The lack of immunogenicity and pharmacodynamics data for the fourth haemagglutinin (B strain) and the quadrivalent vaccine is considered acceptable based on the clinical experience with the quadrivalent vaccine. No particular safety issues were identified in the nonclinical studies that would be of concern for human use. All nonclinical data relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

In line with the EMA “Guideline on Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005), no pharmacokinetic studies were conducted, which is acceptable. Pharmacodynamic studies for vaccines are essentially comprised of the immunogenicity studies that characterise the immune response to the vaccine (Guideline on Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005).
Mechanism of action:
Supemtek, a quadrivalent recombinant influenza vaccine (RIV4) contains recombinant haemagglutinin proteins of the four strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine. It provides active immunisation against four influenza virus strains: an A/(H1N1) strain, an A/(H3N2) strain, and two B strains (one from each lineage: B/(Victoria) and B/(Yamagata)). This vaccine induces humoral antibodies against the haemagglutinins included in the vaccine.
The most relevant immune response consists of the production of sufficient amounts of anti-haemagglutinin immunoglobulin G (IgG) antibodies. These antibodies bind to influenza viruses invading the respiratory tract and neutralise them before the viruses reach the cells of the respiratory epithelium (which are the primary host for viral replication) thus preventing cell infection, viral replication and disease. Haemagglutination inhibition (HI) antibody titres ≥ 1: 40 have been associated with protection from influenza illness in up to 50% of subjects in some human challenge studies, although no definite correlate of protection has been determined.[4]

6.2 Dose Finding and Dose Recommendation

Supemtek has a higher haemagglutinin antigen content compared to the standard dose seasonal influenza vaccines, namely 45 µg per antigen compared to 15 µg per antigen in the inactivated influenza vaccines.

No formal dose-finding studies have been performed with Supemtek. The clinical development programme was based on the recombinant trivalent influenza vaccine (RIV3). Supemtek is equivalent to RIV3 with regard to the quantity of each HA antigen and the excipients, but contains a second B strain.

6.3 Efficacy

Three controlled phase III clinical trials were submitted in support of the marketing authorisation.
Studies PSC12 and PSC16 evaluated the safety and immunogenicity of RIV4 in adults aged ≥ 18 years, and efficacy in adults 50 years of age and older, in comparison to an inactivated, standard dose quadrivalent influenza vaccine (IIV4), approved in Switzerland.
Studies PSC12 and PSC16 evaluated the safety and efficacy of RIV4 in adult subjects, and were considered as the pivotal studies.
The study vaccines used in the pivotal studies were produced at different manufacturing sites as the commercialized vaccine, and comparability was shown based on quality attributes.
Both pivotal studies were conducted in the USA in the 2014/2015 influenza season. The vaccines contained: A/California/ 07/2009 (H1N1), A/Texas/50/2012 (H3N2) strains, and B/Brisbane/60/2008 from the Victoria lineage, and B/Massachusetts/2/2012 from the Yamagata lineage.

Study PSC04 was conducted with RIV3 (FluBlok) to evaluate the efficacy relative to placebo in healthy adults aged 18-49 years. Study PSC04 was considered supportive.

[4] The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses - PMC (nih.gov)

Study PSC12 was a modified double-blind (vaccine administrator not blinded), randomised, active-controlled, parallel-design, multicentre study.
The primary objective was to compare the clinical efficacy of RIV4 with that of IIV4, with respect to the attack rates of rtPCR-confirmed, protocol-defined influenza-like illnesses (ILIs) caused by any influenza viral types/subtypes, starting at least 14 days after vaccination.
The secondary objectives were to compare the protective efficacy in the prevention of respiratory illness and influenza infection starting at least 14 days after vaccination among RIV4 recipients vs. IIV4 recipients using several alternative case definitions.
In addition, immunogenicity - post-vaccination HAI geometric mean titres (GMTs) and seroconversion rates for all four antigens - safety and reactogenicity of RIV4 to IIV4 were compared in a preselected subset of subjects.

A total of 8,963 subjects were randomised 1:1 to receive a single dose of RIV4 (4,474 subjects) or IIV4 (4,489 subjects).
A high rate of subjects (>94%) completed the study, and the two vaccine groups were balanced with respect to subject retention rates and reasons for early discontinuation and major protocol deviations.
The study enrolled medically stable adults aged 50 years or older. The mean age of subjects was 62.7 years in the RIV4 group and 62.6 years for IIV4. 10% of the total enrolled subjects were over 75 years old, and more than 100 subjects were older than 85. Females, white/Caucasians, and non-Hispanics comprised the majority of the study population (58.4%, 80.2%, and 95.1%, respectively).
For the safety population, demographic characteristics were balanced between the study groups.
More female subjects were enrolled in the study, similarly between both vaccine groups (58.5% and 41.5% in the RIV4 group and 58.4% and 41.6% in the IIV4 group).
A similar rate of subjects reported having received an influenza vaccine in the previous season in both vaccine groups (RIV4 53.4%, IIV4 53.9%).
Medical history and the use of prior medications were balanced between the vaccine groups.

Results:
Primary efficacy analysis of the study PSC12 was based on the numbers of protocol-defined influenza-like illnesses with rtPCR-positive nasopharyngeal swabs detecting influenza virus of any strain with onset at least 14 days after vaccination. Non-inferiority criteria, for which the study was powered, was the lower bound of the 95% confidence interval for relative vaccine efficacy (rVE) of -20%.
Protocol-defined ILI was defined as at least one of the respiratory symptoms of sore throat, cough, sputum production, wheezing, and difficulty breathing, accompanied by at least one of the systemic symptoms of fever >37.2, chills, tiredness, headache and myalgia.
Data from 8,604 adults yielded attack rates of rtPCR-confirmed protocol-defined ILI of 2.2% (n=96) among 4,303 RIV4 subjects and 3.2% (n=138) among 4,301 IIV4 subjects. The rVE was +30% with 95% CI: 10; 47%. Thus, RIV4 met the pre-specified, although not stringent, criterion for non-inferiority.
Based on the time to rtPCR-confirmed protocol-defined ILI, the difference between attack rates in RIV4 recipients compared with IIV4 recipients became apparent 3-4 weeks after vaccination and persisted throughout the study.

Secondary and post-hoc efficacy analyses further evaluated the rVE in the efficacy population, although some of the pre-planned secondary analyses could not be performed because the antigenic similarity of cultured viruses to the vaccine strains could not be assessed in this trial.
15 samples from subjects who met the criteria for protocol-defined ILI were subsequently confirmed by culture. The rVE for culture-confirmed protocol-defined ILI was 43% (95%CI 21, 59%).
The time to culture-confirmed protocol-defined ILI cases showed a similar pattern as the time to rtPCR-confirmed protocol-defined ILI cases.
ILI defined by the Centers for Disease Control and Prevention (CDC) was considered more stringent than the protocol-defined ILI, as it required elevated body temperature (over 37.8 °C) in conjunction with upper respiratory symptoms of sore throat and/or cough. rVE against rtPCR-confirmed CDC-defined ILI was 32% (95%CI 8, 54%).

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Thus, the non-inferiority criteria were also met by the rVEs for rtPCR-confirmed and culture-confirmed CDC-defined ILI.
The rVEs for influenza A and B strains separately were also assessed post-hoc. rVE for RIV4 against rtPCR-confirmed protocol-defined ILI caused by influenza A was 36% (95%CI 14, 53%), with a relative risk of 0.64.
For B strains, the time to rtPCR-confirmed protocol-defined ILI curves were overlapping, the rVE was 4% (95%CI -72, 46).
Of note, this analysis does not include four subjects who were hospitalised with documented influenza A infection, three of whom had received IIV4 and one RIV4.
For a tabulated presentation of the above results, please refer to the information for healthcare professionals in the appendix (Table 3).

CDC epidemiological data for the 2014/2015 influenza season indicated that influenza A (H3N2) viruses predominated and that most influenza A/H3N2 viruses were antigenically dissimilar, while A/H1N1 and B viruses were antigenically similar to the vaccine antigens. The estimated vaccine effectiveness based on the CDC report indicated low vaccine efficacy for this season (for all ages: 19%). Thus, a relative vaccine efficacy compared to this unusually low effectiveness is inconclusive. However, regarding the rVE against the A strains, especially taking into account the mismatch for A/H3N2, this is considered an acceptable result. No conclusive efficacy could be shown in regard to the B strains, especially with regard to the B/Victoria as, based on epidemiological data, 70% of the circulating B strains were B/Yamagata.

Immunogenicity endpoints compared both seroconversion rates and post-vaccination ratios of HAI GMT on day 28 post-vaccination. Non-inferiority was assessed based on the Center for Biologics Evaluation and Research (CBER) criteria.
The immunogenicity population included a total of 614 subjects, 314 in the RIV4 and 300 in the IIV4 group. The mean age was 62.2 years in the RIV4 and 61 years in the IIV4 group, and more subjects older than 65 years of age were included in the RIV4 group than in the IIV4 group (37.7% to 30.3%). More females were included than males, but were balanced between vaccine groups (RIV4: 58.9% to IIV4: 59%). The rate of subjects reporting to have received an influenza vaccine in the previous season was comparable between the groups (RIV4: 53.4 %, IIV4: 53.9%).
RIV4 met the non-inferiority CBER criteria, defined as the upper bound of the 95% CI for the difference in seroconversion rate (SCR IIV4 minus SCR RIV4 should not exceed 10%) for strains A/H3 and B/Yamagata, but did not demonstrate non-inferiority for A/H1 or B/Victoria.
The non-inferiority of the post vaccination HAI GMTs, defined as the upper bound of the two-sided 95% CI on the ratio of the GMTs (GMT IIV4/GMT RIV4) should not exceed 1.5. Supemtek demonstrated non-inferiority for the two A strains and for B/Yamagata, although the non-inferiority criterion was not met for B/Victoria. Of note, non-inferiority of the post-vaccination HAI GMT ratio was also not met for B/Victoria in Study PSC16 in young adults (see below).
For a tabulated presentation of the immunogenicity data from Study PSC12 please refer to the information for healthcare professionals in the appendix (Table 2.)
Seroconversion rates assessed by age category for Supemtek demonstrated that only strain A/H3 met the CBER criteria for seroconversion rates in both age groups: below 65 years (the lower bound of the 95% CI>40%) of age and over 65 years (the lower bound of the 95% CI>30%).
In the age group of 50-64 years, strain A/H1 also fulfilled the criterion.
Of note, IIV4 met the CBER seroconversion criteria in the 50-64 year-old groups for H1 and H3, but for the over 65 year-old population did not meet the criteria for any of the strains.

Study PSC16 is a modified double-blind, randomised, active-controlled, multicentre study to compare the immunogenicity and safety of Supemtek versus IIV4 in healthy, medically stable adults 18-49 years of age.
A total of 1,350 ambulatory adults 18-49 years of age in good health or medically stable were enrolled in the study. Subjects were randomised 3:1 to receive either RIV4 or licensed IIV4.
Primary objectives:

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(1) to demonstrate non-inferior immunogenicity of the four antigens in the RIV4 to the corresponding antigens in IIV4 based on the ratio of post-vaccination HAI geometric mean titres (GMT) to each of the four antigens and the difference in HAI seroconversion rates to the same four antigens. Evaluations utilised CBER criteria for non-inferiority of HAI geometric mean titres (GMTs) and seroconversion rates.
(2) to compare the safety profiles of RIV4 and IIV4.
The secondary objective was to evaluate the seroconversion rates and percentages with post-vaccination titres ≥40 against the four rHA antigens contained in the quadrivalent formulation with respect to CBER criteria.
Of the 1,350 subjects who were enrolled and randomised, all received a dose of study vaccine, with 1,011 subjects in the RIV4 group and 339 subjects in the IIV4 group.
A high rate of subjects completed the study. Of the 63 subjects who did not complete the study, 49 were lost to follow-up, 11 withdrew consent and 3 terminated for other reasons. No subject discontinued due to an adverse event.
Subject disposition and the proportion of subjects completing the study were balanced between the groups.
The rate of subjects with a protocol deviation excluding them from the immunogenicity analysis was approx. 2 times higher in the control, IIV4, group.
The mean age of subjects was 33.3 years in the RIV4 group and 34.0 years in the IIV4 group. Approx. 2/3 of the subjects were female, although they were balanced between groups.
Medical history and concomitant medication were balanced between the groups.

Results:
Primary endpoints:
Non-inferiority, defined as an upper bound of the 95% confidence interval for the difference in SCR [IIV4 minus RIV4] ≤10%, was demonstrated for seroconversion among the RIV4 recipients for A/H1/California, A/H3/Texas and B/Massachusetts. The seroconversion rate to B/Brisbane among RIV4 was lower compared to IIV4 and did not meet the criterion for non-inferiority. The difference was even higher for males.
For A/H3/Texas, the seroconversion rate was notably higher (upper bound of 95% confidence interval for the difference in SCR [IIV4 minus RIV4] of < 0) among RIV4 recipients as compared to IIV4 recipients.
For A/H1/California, A/H3/Texas and B/Massachusetts the post-vaccination GMTs were non-inferior by the criterion of an upper bound of the 95% confidence interval around the ratio of GMT IIV4/GMT RIV4 ≤1.5. However, the RIV4 group did not meet the criterion for non-inferiority for B/Brisbane.
Of note, a lower immune response induced by the B/Brisbane was also observed in Study PSC12 conducted with adults over 50 years of age.
Secondary endpoints:
The CBER criterion for an acceptable magnitude of seroconversion rates (lower bound of the 95% confidence interval ≥40%) measured at Day 28 post vaccination was met for the RIV4 group for A/H1/California, A/H3/Texas and B/Massachusetts. The criterion was not met for B/Brisbane.
For IIV4 seroconversion, the criterion was met for all 4 antigens.
The CBER criterion for the proportion of individuals who have a post-vaccination HAI titre ≥40, also referred as the seroprotection rate, in adults <65 years of age is defined as the lower bound of the 95% confidence interval that meets or exceeds 70%. This criterion was reached by all of the strains for IIV4 and for three strains for RIV4. In the RIV4 subjects for the B/Brisbane strain, the lower bound of the 95% CI was 61.2, resulting in failure to meet the criterion.
The CBER criterion for the rate of seroconversion and post-vaccination HI titre ≥40 for the B/Brisbane strain was not reached in the RIV4 group.
As the expectation was that non-inferiority would be demonstrated for all eight comparisons (seroconversion rates and post-vaccination HAI GMT for all 4 strains), and that the primary objective would therefore be declared as met, the study did not meet its primary endpoints.
A possible explanation presented by applicant for the lower immune response induced by the B/Victoria strain was that the study population was naïve to the B/Victoria strain, as indicated by the low baseline GMTs. However, the 18-49 year-old subjects with low baseline HI titres (naïve persons)

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normally tend to have a stronger immune response with high seroconversion rates, not as seen with the B/Victoria strain in Supemtek.
For a tabulated presentation of the immunogenicity results from Study PSC016, please refer to the information for healthcare professionals in the appendix (Table 1).

Study PSC04 was considered to be the key supportive study. It evaluated immunogenicity, safety, reactogenicity, efficacy, effectiveness and lot consistency of FluBlok, the trivalent recombinant influenza vaccine, in healthy adults aged 18 to 49 years, in the 2007/2008 influenza season.
A total of 4,648 eligible subjects were randomised at a 1:1 ratio to one of two groups of FluBlok (and was further stratified into three lots, A, B and C) or to saline placebo.
The study population was mostly healthy adults 18-49 years of age in a good general state. Subjects with chronic conditions that are usually considered as an at-risk group and indicated for influenza vaccination were excluded, as were pregnant women. The rate of subject discontinuation was high: 12.4%, 89% of whom were lost-to follow-up. There was no meaningful difference among the treatment groups in the baseline characteristics.
The three lots investigated did not achieve the pre-defined criteria for lot-to-lot consistency due to the lower GMT ratios observed for the A/H3 strain.
Immunogenicity results showed that the lower bound of the 2-sided 95% CI for the seroconversion rates against the three antigens all exceeded the CBER criterion of ≥40% (73.8% for H1, 76.3% for H3, and 48.1% for B). And the lower bound of the 2-sided 95% CI for the seroprotection rates for all three antigens also exceeded the CBER criterion of ≥70% (96.7% for H1, 94.1% for H3, and 93.4% for B).
The CBER criteria for seroconversion rates were not met for the B strain in the subgroup of subjects (N=83) who reported having been vaccinated in the previous season.
Efficacy results are presented in the information for healthcare professionals in the appendix (Table 4).

6.4 Safety

As the study populations were different for the pivotal studies PSC 12 and PSC 16, a pooled safety analysis was not available. The safety profile of RIV4 is discussed separately for the studies.
The safety population from the two studies included 10,002 adults aged 18 years and older**.** A total of 5,326 subjects received RIV4 in the two studies PSC12 and PSC16: 998 adults 18 to 49 years of age in study PSC16, 2,569 adults from 50 to 64 years of age in study PSC12, and 1,759 elderly ≥ 65 years of age in study PSC12.
The use of RIV4 was not studied in pregnant or breastfeeding women.

Study PSC12
The safety population included all randomised subjects who received a dose of study vaccine and for whom some safety data were available.
The most common local reactogenicity events were injection site tenderness (RIV4 34.3%, IIV4 37.1%) and pain (RIV4 18.9%, IIV4 22.0%), with mostly mild or moderate severity.
Injection site redness was somewhat more frequent in RIV4 recipients, but these reactions occurred in fewer than 3% of subjects in either group, and most were graded as mild.
Grade 4 injection site reactions were very infrequent, but numerically more frequent among IIV4 recipients.
In both treatment groups, most injection site reactions were reported significantly more frequently among whites, females, non-Hispanics and younger subjects (aged 50-64 years) than among blacks, males, Hispanics or older adults (≥ 65 years). Gender and inverse age differences in reactions to vaccine injections are well recognised.
Approximately 25% of the study population experienced at least one solicited systemic AE.
The most common solicited systemic symptoms were headache (RIV4 12.7%, IIV4 13.5%), fatigue (RIV4 12.2%, IIV4 12.2%), muscle pain (RIV4 8.5%, IIV4 8.8%), and joint pain (RIV4 7.5%, IIV4 8.0%). Rates and severity of systemic reactogenicity events were balanced between groups.

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Fatigue, myalgia and headache were reported significantly more frequently by females, regardless of the vaccine received.
All systemic reactions were significantly less frequent among older subjects (≥ 65 years) than among the younger adults (50-64 years).
The frequency of fever (RIV4 0.4%, IIV4: 0.5%) was low, and was mostly mild or moderate.
Rates of unsolicited adverse events were similar in both vaccine groups, with no clinically concerning or unexpected events occurring predominantly during the 28 days of follow-up after vaccine administration. Myalgia was reported for slightly more subjects in the RIV4 group.
No events in RIV4 recipients were considered life threatening (Grade 4).
For most System Organ Classes of AEs, significantly more events were reported by female subjects than by male subjects, but the gender effect was similar in each vaccine group.
The AEs that might represent hypersensitivity were similar in both vaccine groups.
There were 20 deaths throughout the duration of the study, eight among RIV4 recipients and 12 among IIV4 recipients.
277 serious adverse events (SAEs) were reported overall during the six months of follow-up after vaccination, 145 (3.4%) and 132 (3.0%) subjects in the RIV4 and IIV4 treatment groups, respectively.
No relevant differences were observed in the number and type of medically-attended SAEs in the 28 days or 6 months following vaccination. The rate of medically-attended adverse events through day 28 was similar for both groups (RIV4:4.8% IIV4:5.4%).
None of the SAEs or medically-attended adverse event (MAEs) were considered to be related to the study vaccine.
In addition to the 20 deaths reported above, one additional subject discontinued the study due to an adverse event after receiving RIV4. The event was described as a psychiatric disorder diagnosed as an “adjustment disorder.” The event was not considered to be related to the study vaccine.

Study PSC016
Local injection site reactogenicity was similar in incidence and severity between the treatment groups, with the exception of erythema and, to a lesser extent, swelling. The incidence of erythema (reported as “redness”) at the site of injection (all mild or moderate in severity) was notably higher among RIV4 recipients than among IIV4 recipients (p=0.002).
Within both treatment groups, females had a statistically significantly higher incidence of at least one solicited reactogenicity event compared to males. Also, within both treatment groups, females had a statistically significantly higher incidence of any solicited local reaction, any local pain and any local tenderness. In addition, within the RIV4 group, female recipients had a statistically significantly higher incidence of redness and swelling.
Systemic events of reactogenicity were mostly mild-to-moderate in severity, and none were statistically significantly different between treatment groups. The most common systemic symptoms were headache (RIV4 20.3%, IIV4 21.1%), fatigue (RIV4 16.5%, IIV4 16.6%), muscle pain (RIV4 12.8, IIV4 11.7%), and joint pain (RIV4 9.5%, IIV4 10.2%). The percentage of subjects reporting fever was higher in the RIV4 group than the IIV4 group (1.5% to 0.6%)
Unsolicited adverse events reported through day 28: The most common unsolicited events (based on preferred terms), regardless of relatedness to study vaccine, that occurred in ≥ 1% of subjects in either vaccine group were nasopharyngitis, upper respiratory tract infection, sinusitis, cough and headache. All were reported in less than 2% of subjects and with a similar rate for both vaccine groups.
There were no deaths during the study.
Fifteen serious adverse events were reported overall in 12 subjects, 10 (1.0%) of the RIV4 recipients and 2 (0.6%) of the IIV4 recipients, during the 6-month period of follow-up. Of note, 2 subjects (aged 38 and 44) had a myocardial infarction in the RIV4 arm within 5 months after vaccination. One of the patients had a history of hypertriglyceridaemia and type 2 diabetes, but the case data for the other subject was very limited. RIV4 recipients experienced three SAEs, while no IIV4 recipients experienced SAEs during the 28 days post vaccination.
No SAEs were considered to be related to the study vaccine by the investigator or the sponsor.

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Medically-attended AEs during the 6 months of follow-up after vaccination were reported for 80 subjects (8.0%) in the RIV4 group and 24 subjects (7.2%) in the IIV4 group.
No subjects reported having experienced anaphylaxis or other hypersensitivity events.
A total of 8 women, all RIV4 subjects, became pregnant subsequent to vaccination in study PSC16. None was pregnant at the time of vaccination, and one pregnancy case was reported outside the clinical study period. One woman experienced a miscarriage and the others delivered full-term, healthy infants.

In summary, based on the results of Study PSC012 and PSC016, the safety profile of RIV4 can be considered comparable to the safety profile of IIV4.

Post-marketing safety data regarding Supemtek:
According to the initially provided post-marketing data eleven serious cases of standardised MedDRA Queries (SMQ) (broad) anaphylaxis and SMQ (broad) angioedema were reported for RIV4, which corresponded to 1.13 serious cases per million doses. Based on the additionally requested and provided post-marketing data, the rate of SMQ anaphylaxis and angioedema for RIV4 can be considered acceptable and approximately similar to other influenza vaccines.
Anaphylaxis is an identified risk for Supemtek, and the safety profile will be monitored via routine pharmacovigilance measures.

Safety data with RIV3:
Further safety data came from Study PSC04 and PSC 13, which was a post-marketing observational study of safety following vaccination with Flublok compared to licensed IIV in adults conducted by the Kaiser Permanente Vaccine Study Center. From November 2015 through March 2016, Kaiser Permanente Northern California (KPNC) vaccinated 21,976 adult subjects with Flublok.
There were no specific safety concerns regarding the use of Flublok in adults based on the results of the above studies with RIV3.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Vaccination against influenza is the cornerstone public health intervention to reduce the annual burden of seasonal influenza epidemics, although protection - especially in the elderly - is incomplete. Worldwide, several standard-dose (15 µg per haemagglutinin) egg-based and cell based trivalent and quadrivalent seasonal influenza vaccines are available, as are adjuvanted or high-dose influenza vaccines indicated for the elderly.
This is the first application concerning the marketing authorisation request for a recombinant seasonal influenza vaccine in Switzerland.
Supemtek, a quadrivalent recombinant influenza vaccine (RIV4), is manufactured with recombinant DNA technology, using a baculovirus expression system in a continuous insect cell line that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda*. It contains a higher dose of the high-purity antigens: three times more HA than standard-dose seasonal influenza vaccines; the active substance is 45 µg in each case of recombinant haemagglutinin (rHA) of A strains (A/H1N1 and A/H3N2) and B strains (from Victoria and Yamagata lineages).
The development programme for Supemtek built on that for the trivalent formulation (RIV3, Flublok). Flublok was available in the USA from 2013 until it was discontinued in 2018. Then, RIV4, under the name of Flublok Quadrivalent, was approved by the FDA in 2016.
The initial marketing authorisation request for Supemtek was under review by the EMA as a centralised procedure at the start of this application process, and was approved on 16 November 2020.

The submitted data package (including two pivotal studies with RIV4 and a supportive study with RIV3 and further post-marketing data) is sufficient for the assessment of the marketing authorisation request.

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In Study PSC12, Supemtek showed non-inferior relative vaccine efficacy (rVE) preventing rtPCR-confirmed protocol-defined influenza-like illness beginning at least 14 days after vaccination compared to IIV4 in adults over 50 years of age. Although not a pre-specified endpoint, Supemtek showed superior overall efficacy over IIV4 regardless of the fact that there was a predominant mismatch of strains in that season.
The rVE was most likely driven by the efficacy against A/H3N2, as this was the predominant circulating strain in the trial season. In both pivotal studies, the HI antibody response for A/H3 was markedly higher for Supemtek in all age groups. The strong immune response demonstrated for A/H3 in Supemtek is relevant as A/H3N2 is associated with greater virulence.
The efficacy was confirmed by a key secondary endpoint (culture-confirmed ILI according to the CDC ILI definition) and a post-hoc exploratory endpoint based on all cases of culture-confirmed influenza. Of note, this analysis does not include four subjects who were hospitalised with documented influenza A infection, three of whom had received IIV4 and one RIV4.
Furthermore, non-inferior immunogenicity based on the seroconversion difference and GMT ratio defined by the CBER criteria was demonstrated for A/H3 and B/Yamagata.

In Study PSC16, conducted with healthy adults 18-49 years of age, Supemtek demonstrated non-inferior immune response to IIV4, as measured by HI titres (seroconversion rate difference and GMT ratio) for the A/H1, A/H3 and B/Yamagata strains.
Additionally, the CBER criteria for seroconversion rates and the rates of subjects with an HI titre ≥ 1:40 were met for both A strains and for B/Yamagata in younger adults aged 18-49 years.
In the supportive study PSC04, conducted with healthy adults aged 18 to 49 years, RIV3 was efficacious in preventing culture-positive CDC ILI due to any strain.

The relative vaccine efficacy was evaluated (rVE) in the USA in the 2014/2015 influenza season, when the CDC estimated vaccine effectiveness was unusually low, at 19%.
The rVE was low for the B strains, and efficacy against influenza B/Victoria could not be clearly demonstrated as, in the trial season, the B/Yamagata lineage was dominant among the B strains. The lack of conclusive efficacy left the lower immune response induced by B/Victoria a relevant concern.
In Study PSC16, the non-inferiority for B/Victoria (Brisbane) was not demonstrated. Additionally, CBER criteria for seroconversion and seroprotection rates were not achieved.
The immune responses for B/Brisbane were lower at baseline, also post vaccination, for both treatment groups, although IIV4 achieved the CBER criteria.
In Studies PSC012 and PSC016 B/Victoria (Brisbane) showed consistently low immune response.
The company provided additional requested evidence to the EMA and with the answer to the LoQ arguing that there is no general weakness regarding the immunogenicity of the B/Victoria lineage.
Overall, the argumentation of the applicant regarding B/Victoria strains, including the discussion in the EMA assessment report, is not fully convincing. Typically, most non-previously vaccinated persons, contrary to the discussion of the applicant and EMA, show a better immune response to influenza vaccines compared to previously vaccinated persons. The additional data show that the immune response of the Victoria lineage, when included in RIV4 or RIV3, is comparable with other influenza vaccines, but do not fully alleviate the concerns raised due to the weaker immune response observed in Studies PSC12 and PSC 16. This must be seen in the context of the better response of Supemtek to A/H3 strains, which have high clinical relevance. The findings of the lower GMTs and seroconversion rates for the B/Brisbane/60/2008 strain in Studies PSC 12 and 16 are described in the information for healthcare professionals.
The rVE in the elderly (over 65 years of age) was lower compared to those aged 50-64, which is indeed not an unusual finding. However, in the elderly RIV4 induced a low HI response, and the seroconversion rates and rate of subjects with HI titres ≥ 1:40 did not meet the CBER criteria for the strains included, with the exception of A/H3, which only reached the seroconversion criteria. Of note, the comparator vaccine, IIV4, did not meet the seroconversion or seroprotection criteria for any of the strains included in the elderly population.
Persistence of immunogenicity was not assessed in any of the clinical studies submitted in support of this application.

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Study PSC04 provided some, albeit limited, support based on the efficacy of RIV3 due to the poor match between the circulating and vaccine strains in the 2007/2008 season. The three lots investigated did not achieve the pre-defined criteria for lot-to-lot consistency due to the lower GMT ratios observed for the A/H3 strain. Thus, study PSC04 in principle cannot support lot-to-lot consistency. As the production and production facility have changed since 2007, trust in new process has rely on the acceptance of the Quality dossier.

Based on a safety database of 5,326 subjects receiving RIV4, the safety of RIV4 in adults was generally acceptable and comparable with the safety of the comparator, an approved IIV4.
Local and systemic reactions were consistent with the reactogenicity of influenza vaccines. In both vaccine groups, the most frequently reported local reactions were mild and moderate and included tenderness and pain. The most frequently reported systemic reactions were headache, fatigue and myalgia.
A lower reactogenicity in the elderly compared to younger adults was observed, consistent with other influenza vaccines. Most reactogenicity events were mild to moderate (Grade 1 to Grade 2) in severity and short in duration. Severe (Grade 3) reactions were uncommon.
No deaths or discontinuations due to AEs occurred in Study PSC16 (adults 18-49 years). Twenty subjects died in PSC12 (adults ≥50 years) during the six month follow-up period, compared to 8 subjects in the RIV4 and 12 subjects in the IIV4 group. All deaths were considered to be unrelated to the study vaccine. Of note, 2 subjects (aged 38 and 44 years) in Study PSC16 had a myocardial infarction in the RIV4 arm within 5 months after vaccination. The relevance of this finding is currently not clear, although there were no clear hints in other studies on the cardiovascular risk even in the elderly.
In the 18-49 year-old adults, SAEs were reported in slightly more RIV4 subjects (ten (1.0%)) than IIV4 subjects (two (0.6%)) during the six months post-vaccination period. Three (0.6%) of the RIV4 recipients experienced three SAEs, while no IIV4 recipients experienced SAEs during the 28 days post vaccination. None of the SAEs appeared to be related to the study vaccines.
In subjects ≥ 50 years, the SAEs were similar between the vaccine groups during the six-month study period and for the post-vaccination 28 days. Other than an imbalance of ILIs (more in IIV4 recipients), medically-attended events (MAEs) were balanced between the treatment groups.
RIV4 was not associated with a greater risk of clinically significant acute hypersensitivity in the safety database of 5,326 adults.
According to the initially provided limited post-marketing data, an approx. double the rate of anaphylaxis for Supemtek was observed compared to the usually accepted rate of anaphylaxis for vaccines and data from the literature.
With the additionally submitted post-marketing data, based on a total of 9,677,760 doses of RIV4 distributed worldwide, the rate of SMQ anaphylaxis and angioedema based on the post-marketing data for RIV4 can be considered acceptable and approximately similar to other influenza vaccines (1.13 serious cases per million doses).
The applicant provided further post-marketing data and the Periodic Benefit Risk Evaluation Report based on 21,400,800 exposures. This showed no new safety concerns and confirmed that the rate of anaphylaxis and angioedema was approximately in the range of that for other influenza vaccines.
Anaphylaxis is considered as an identified risk for Supemtek, as included in the *information for healthcare professionals,* and the safety profile of Supemtek will be monitored by routine pharmacovigilance measures.

Supemtek, a quadrivalent recombinant seasonal influenza vaccine (RIV4), is proposed for marketing authorisation for the first time in Switzerland.

Supemtek met the predefined non-inferiority criteria for relative vaccine efficacy (rVE) as compared to the approved inactivated quadrivalent vaccine (IIV4), and demonstrated a lower relative risk of rt-PCR-confirmed protocol-defined ILI (due to all strains) in healthy adults over 50 years of age. The

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efficacy results were mostly driven by the efficacy against the predominant, but non-matching, A/H3N2 strain.
In both pivotal studies, the immunogenicity of RIV4, as measured by the haemagglutination inhibition assay (HI) for the B/Victoria lineage strain, failed the statistical non-inferiority assessment as compared to the quadrivalent inactivated influenza vaccine (IIV4) in adults and the elderly. Furthermore, the immune response, as measured by geometric mean titre (GMT) and seroconversion rate for the B/Brisbane strain, was generally lower, however, for both RIV4 and IIV4 in the two pivotal studies. Other strains included in RIV4 induced an acceptable and for the A/H3N2 strain, even higher immune response compared to IIV4.
The strong immune response demonstrated by the GMTs, seroconversion and seroprotection rates for A/H3 is supportive of the efficacy findings of study PSC12.
Based on the submitted pivotal studies (PSC12 and PSC16), Supemtek induces a weaker immune response to B/Brisbane/60/2008 compared to an IIV4. The additionally provided data for RIV4 and RIV3 containing the same, or a different, strain of the B/Victoria lineage could not fully resolve this issue. This must be seen in the context of the better response of Supemtek to the A/H3 strains, which have clinically high relevance and are more virulent, resulting in higher morbidity. Post-marketing effectiveness studies will be essential for further clarity.

The safety profile of RIV4 is considered acceptable and comparable with an IIV4 based on the submitted clinical trial results. The rate of SMQ anaphylaxis and angioedema based on the post-marketing data for RIV4, can also be considered acceptable and approximately similar to that for other influenza vaccines. Routine pharmacovigilance monitoring will take place.

The benefit/risk profile of Supemtek for active immunisation in adults aged 18 years and over for the prevention of influenza caused by the influenza virus subtypes included in the vaccine can be considered positive.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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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.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Supemtek, solution for injection in pre-filled syringe, 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 approved and 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.

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▼ 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.

SUPEMTEK

Solution for injection in pre-filled syringe.
Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture).

Composition

Active substances

One dose (0.5 mL) contains:
Influenza virus haemagglutinin (HA) proteins, of the following strains*:

A (H1N1), A (H3N2), B (Yamagata), B (Victoria) according to the annual recommendations of the World Health Organization (WHO) recommendation for the Northern Hemisphere.

*Produced by recombinant DNA technology using a baculovirus expression system in a continuous insect cell line that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda.*

Excipients

Polysorbate 20 (E 432)
Sodium chloride: 150 mM
Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, dodecahydrate
Water for injections
Contains 1.84 mg Sodium per dosis (0.5 mL).
Supemtek may contain traces of octylphenol ethoxilate.

Pharmaceutical form and active substance quantity per unit

Solution for injection (0.5 mL) in pre-filled syringe. One dose contains 45 µg hemagglutinin of each of the four influenza virus strains.
Supemtek is clear, colourless and essentially free of visible particles.

Indications/Uses

Supemtek is indicated for active immunization in adults aged 18 years and over as part of the prevention of influenza caused by the two influenza A virus subtypes and the two influenza B virus subtypes contained in the vaccine.

Supemtek should be used in accordance with official recommendations.

Dosage/Administration

In adults of 18 years of age and older: one dose of 0.5 mL.

Paediatric population

Safety and efficacy of Supemtek have not yet been established in children under 18 years of age. No data are available.

Mode of administration

Administration should be carried out by intramuscular (IM) route preferably in the deltoid muscle.
The vaccine must not be injected intravascularly and must not be mixed with other vaccines in the same syringe.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.
For instructions on the handling of the vaccine before administration, see section “Instructions for handling”.

Contraindications

Hypersensitivity to the active substances, to any of the excipients or to any components that may be present as traces such as octylphenol ethoxilate.

Warnings and precautions

Prior to vaccination, check the medical history (especially with regard to previous vaccinations and any adverse effects).
Supemtek must not be administered intravascularly under any circumstances.
Vaccination should be postponed in patients with acute febrile illness until the fever is resolved.
Hypersensitivity:
Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.
Thrombocytopenia and coagulation disorders:
As with other vaccines administered intramuscularly, the vaccine should be administered with caution to subjects with thrombocytopaenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.
Syncope:
Syncope can occur following or even before any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury due to fainting and to manage syncope.

Protection:
As with any vaccine, vaccination with Supemtek may not protect all vaccinees.
Supemtek is used to protect against those influenza virus strains from which the vaccine is made.
Immunodeficiency:
Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient to prevent influenza.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially “sodium free”.

Interactions

No studies on concomitant administration with other vaccines were performed.
If Supemtek is to be given at the same time as another injectable vaccine, the vaccines should never be administered at the same injection site.

Pregnancy, lactation

Pregnancy

Clinical study data on the use of Supemtek in pregnant women are not available.
One animal study performed with trivalent recombinant influenza vaccine did not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development or early post-natal development.
An assessment of the risks and benefits should be performed by a health care professional before administering Supemtek to a pregnant woman.

Lactation

No data are available on breastfed neonates/infants whose mothers were vaccinated with Supemtek during the breastfeeding period. It is not known whether Supemtek vaccine is excreted in human milk.
An assessment of the risks and benefits should be performed by a health care professional before administering Supemtek to a nursing woman.

Fertility

No human fertility data are available.
The animal study with trivalent recombinant influenza vaccine did not indicate harmful effects on female fertility.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

Supemtek has been administered to and safety data collected from 998 adults 18-49 years of age (Study PSC16) and 4328 adults 50 years of age and older (Study PSC12).
The most common reactions occurring after vaccine administration were injection-site reactions (tenderness and pain) reported overall by 48 % and 37 % of study participants 18-49 years of age receiving Supemtek respectively. In study participants 50 years of age and older, injection site tenderness was reported by 34 % and injection site pain reported by 19 %.
The severity of the reactions was mild to moderate. Onset usually occurred within the first 3 days after vaccination. All resolved without sequelae.
The adverse events are ranked in the text version by MedDRA system organ class under headings of frequency using the following convention:
Very common (≥ 1/10);
Common (≥ 1/100, < 1/10);
Uncommon (≥ 1/1,000, < 1/100);
Rare (≥ 1/10,000, < 1/1,000);
Very rare (< 1/10,000),
Frequency not known (adverse reactions from post-marketing experience; cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Immune system disorders

Frequency not known: Hypersensitivity including anaphylaxis and anaphylactic reaction

Nervous system disorders

Very common: Headache (13 %), Fatigue (12 %)
Rare: Dizziness
Frequency not known: Guillain-Barré Syndrom(7)

Respiratory, thoracic and mediastinal disorders

Uncommon: Cough, Oropharyngeal pain

Gastrointestinal disorders

Common: Nausea
Uncommon: Diarrhoea(4)

Skin and subcutaneous tissue disorders

Uncommon: Pruritus(2,4) , Dermatitis(4,5) , Rash(4,5)
Rare: Urticaria(4,6)

Musculoskeletal and connective tissue disorders

Very common: Myalgia(1) (9 %), Arthralgia (1) (8 %)

General disorders and administration site conditions

Very common: Local tenderness (34 %), Local pain (19 %)

Common: Firmness / Swelling, Redness, Fever [2,3], Shivering / Chills,

Uncommon: Flu-like symptoms[4,6], Injection site pruritus[4]

[1] Common in adults 50 years of age and older.
[2] Rare (≥ 1/10,000 to < 1/1,000) in adults 50 years of age and older.
[3] ≥38.0° C (100.4° F).
[4] Reported as unsolicited adverse reaction.
[5] Not reported in adults 50 years of age and older.
[6] Not reported in adults 18-49 years of age.
[7] Reported from post-marketing surveillance, no causal relationship established.

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

No data regarding overdosage are available.

Properties/Effects

ATC code

J07BB02

Mechanism of action

Supemtek is intended to provide active immunization against the four influenza virus strains (two A subtypes and two B subtypes) contained in the vaccine.

Pharmacodynamics

A correlation of specific hemagglutinin-inhibiting (HAI) antibody titers following the use of inactivated influenza virus vaccines on the one hand and protective efficacy against influenza on the other has not been established, but HAI antibody titers are used as a measure of vaccine activity. Some provocation studies in humans demonstrate an association between HAI antibody titers of ≥ 1:40 and a 50 % reduction of risk of influenza illness.

Because circulating strains of influenza virus are constantly changing, the strains selected for the vaccine are reviewed annually by the WHO.

Immunogenicity

Supemtek was evaluated in healthy adults of 18-49 years of age in a randomized, observer-blind, active controlled, multi-center trial for non-inferiority in immunogenicity conducted during the 2014-2015 influenza season in the United States (study PSC16).

In the study PSC16, subjects received Supemtek (N=998) or an egg-based quadrivalent inactivated influenza vaccine (IIV4) (N=332). Immunogenicity was assessed before and 28 days after administration of a single dose of study vaccine.

Haemagglutination inhibition (HAI) geometric mean titers (GMTs) were determined for the two vaccine groups for each vaccine antigen. Immunogenicity was compared by calculating the difference in seroconversion rates (SCR) and the ratios of GMTs of Comparator to Supemtek. Seroconversion was defined as either a pre-vaccination HAI titer of < 1:10 and a post-vaccination HAI titer of ≥ 1:40, or a pre-vaccination HAI titer of ≥ 1:10 and a minimum 4- fold rise in post vaccination HAI titer, at Day 28.

Study PSC16 had two co-primary endpoints: GMTs and Day 28 HAI seroconversion rates for each of the four antigens contained in the study vaccines.

Success in meeting the GMTs endpoint was pre-defined as an upper bound (UB) of the two-sided 95% CI of $GMT_{Comparator}$ / $GMT_{Supemtek}$ ≤ 1.5. Supemtek met the success criterion for GMTs for three of the four antigens but did not meet the success criteria for the B/Victoria lineage antigen (Table 1). Antibody titres against the B/Victoria were low in both vaccine groups.
Success in meeting the seroconversion rate (SCR) endpoint was pre-defined as an upper bound (UB) of the two-sided 95 % CI of SCR Comparator – SCR Supemtek ≤ 10%. Supemtek met the success criterion for SCRs for three of the four antigens (Table 2), but not for the B/Victoria lineage. The HAI response to the B/Victoria lineage antigen was low in both vaccine groups.

Table 1: Comparison of Day 28 Post-Vaccination Geometric Mean Titers (GMT) and Day 28 Seroconversion Rates for Supemtek and Comparator in Adults 18-49 Years of Age, Study PSC16 (Immunogenicity Population) [1,2,3]

Influenza Strain	Post-vaccination GMT		GMT Ratio
	Supemtek N=969 (95% CI)	Comparator N=323 (95% CI)	Comparator over Supemtek (95% CI)
A (H1N1)	493 (460; 527)	397 (358, 441)	0.81 (0.71, 0.92)

A (H3N2)	748 (700; 800)	377 (341, 417)	0.50 (0.44, 0.57)
B (Yamagata)	156 (145; 168)	134 (119, 151)	0.86 (0.74, 0.99)
B (Victoria)	43 (40; 46)	64 (57, 71)	1.49 (1.29, 1.71)
A (H1N1)	66.7 (63.6, 69.6)	63.5 (58.0, 68.7)	-3.2 (-9.2, 2.8)
A (H3N2)	72.1 (69.2, 74.9)	57.0 (51.4, 62.4)	-15.2 (-21.3, -9.1)
B (Yamagata)	59.6 (56.5, 62.8)	60.4 (54.8, 65.7)	0.7 (-5.4, 6.9)
B (Victoria)	40.6 (37.4, 43.7)	58.2 (52.6, 63.6)	17.6 (11.4, 23.9)
A (H1N1)	98.2 (97.2, 99.0)	99.1 (97.3, 99.8)	-
A (H3N2)	99.7 (99.1, 99.9)	99.1 (97.3, 99.8)	-
B (Yamagata)	91.0 (89.0, 92.7)	92.0 (88.4, 94.7)	-
B (Victoria)	64.3 (61.2, 67.3)	79.6 (74.8, 83.8)	-

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

CI: Confidence Interval; GMT: Geometric Mean Titer; SCR: Seroconversion rate; Seroprotection: Subject with titers >= 40 (1/dil)

[1] HI titers were assayed using egg-derived antigens.

[2] Comparator was an egg-based quadrivalent inactivated influenza vaccine.

[3] Seroconversion was defined as either a pre-vaccination HAI titre of < 1:10 and a post-vaccination HAI titre of ≥ 1:40 or a pre-vaccination HAI titre of ≥ 1:10 and at least a 4-fold increase in the post-vaccination HAI titre on day 28.

These immunogenicity data provide supportive information for the 18-49 years of age group in addition to vaccine efficacy data available in adults ≥ 50 years of age (see Clinical Efficacy).

Table 2: Summary of HAI Antibody Response to Supemtek for Each Strain in Adults 50 Years of Age and Older (Study PSC12), 28 days after vaccination- Immunogenicity Analysis Set

	Adults ≥50 years		
	All* N=314	Adults 50-64 years N=196	Adults ≥65 years N=118
GMT post-vaccination (95% CI)			
A/California/7/2009 (H1N1)	190 (164; 221)	279 (232; 335)	101 (81.6; 126)

A/Texas/50/2012 (H3N2)	522 (462; 589)	603 (515; 705)	411 (342; 494)
B/Massachusetts/02/2012 (Yamagata lineage)	55.5 (48.4; 63.6)	66.6 (56.2;78.8)	41.0 (32.8; 51.2)
B/Brisbane/60/2008 (Victoria lineage)	29.5 (26.0; 33.4)	34.5 (29.5; 40.4)	22.7 (18.6; 27.7)
SCR % (95% CI)			
A/California/7/2009 (H1N1)	44.9 (39.3; 50.6)	55.6 (48.4; 62.7)	27.1 (19.3; 36.1)
A/Texas/50/2012 (H3N2)	54.5 (48.8; 60.1)	62.8 (55.6; 69.5)	40.7 (31.7; 50.1)
B/Massachusetts/02/2012 (Yamagata lineage)	38.9 (33.4; 44.5)	42.9 (35.8; 50.1)	32.2 (23.9; 41.4)
B/Brisbane/60/2008 (Victoria lineage)	21.0 (16.6; 25.9)	25.5 (19.6; 32.2)	13.6 (8.0; 21.1)
GMTR % (95% CI)			
A/California/7/2009 (H1N1)	4.31 (3.71; 5.02)	5.72 (4.67; 7.01)	2.70 (2.21; 3.29)
A/Texas/50/2012 (H3N2)	6.01 (5.03; 7.18)	8.23 (6.49; 10.4)	3.56 (2.82; 4.51)
B/Massachusetts/02/2012 (Yamagata lineage)	3.18 (2.81; 3.59)	3.79 (3.23; 4.45)	2.37 (1.98; 2.84)
B/Brisbane/60/2008 (Victoria lineage)	2.16 (1.94; 2.40)	2.55 (2.21; 2.93)	1.64 (1.41; 1.92)
Seroprotection % (95% CI)			
A/California/7/2009 (H1N1)	90.8 (87.0; 93.7)	94.9 (90.8; 97.5)	83.9 (76.0; 90.0)
A/Texas/50/2012 (H3N2)	99.7 (98.2; 100.0)	99.5 (97.2; 100.0)	100.0 (96.9; 100.0)
B/Massachusetts/02/2012 (Yamagata lineage)	68.2 (62.7; 73.3)	75.5 (68.9; 81.4)	55.9 (46.5; 65.1)
B/Brisbane/60/2008 (Victoria lineage)	49.7 (44.0; 55.4)	55.6 (48.4; 62.7)	39.8 (30.9; 49.3)

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

GMT: Geometric Mean Titer; CI: Confidence Interval; SCR: Seroconversion rate ; GMTR: Geometric Mean Titer ratios of the titers; Seroprotection: Subject with titers >= 40 (1/dil)

*Main population for the immunogenicity analysis

The study PSC16 in adults 18-49 years of age was conducted in parallel to the study PSC12 in adults of 50 years of age and older. These adults 18-49 years of age were vaccinated during the same influenza season (2014-2015 Northern Hemisphere influenza season) and received the same Supemtek formulation (same vaccine strain composition) as adults of 50 years of age and older in the study PSC12. The immune response induced by Supemtek was assessed by the same HAI assay and performed by the same laboratory for both studies. The immunogenicity results in adults 18-49

years of age (Study PSC16) and adults 50 years of age and older (PSC12) are presented in Table 1 and Table 2. Higher HAI antibody response is commonly observed in younger age population.

Clinical efficacy

The efficacy of Supemtek in preventing laboratory-confirmed influenza-like illness (ILI) caused by any strain of influenza was studied and evaluated in adults aged ≥ 50 years during the 2014/2015 influenza season in the United States (Study PSC12).
A total of 8963 healthy, medically stable adults were randomized in a 1:1 ratio to receive a single dose of Supemtek (n=4474) or an egg-based quadrivalent inactivated influenza vaccine (n=4489).
A total of 5412 (60.4 %) subjects were 50-64 years of age, 2532 (28.2 %) were 65-74 years of age and 1019 (11.4 %) were ≥ 75 years of age.
Reverse transcritase polymerase chain reaction (rtPCR)-confirmed influenza was assessed by active and passive surveillance for influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 6 months post- vaccination. ILI was defined as having at least one symptom (no specified duration) in each of two categories of respiratory and systemic symptoms. Respiratory symptoms included sore throat, cough, sputum production, wheezing and difficulty breathing. Systemic symptoms included fever > 99°F (>37°C) orally measured, chills, fatigue, headache and myalgia. A nasopharyngeal swab sample was collected for rtPCR testing from subjects with an episode of ILI. A viral culture was performed on rtPCR-positive samples.

The primary efficacy endpoint of study PSC12 was rtPCR-positive, protocol-defined ILI due to any strain of influenza. Antigenic and phylogenetic evaluations of the similarity (“matching”) of clinical isolates to vaccine antigens were not performed. US epidemiological data for the 2014-2015 influenza season indicated that Influenza A (H3N2) viruses predominated and that most influenza A/H3N2 viruses were antigenically dissimilar while A/H1N1 and B viruses were antigenically similar to vaccine antigens. PCR assay distinguished influenza A H1, A H3 and B viruses. Supemtek met the pre-specified success criterion for non-inferiority to the comparator pre-defined as a lower bound of the two sided 95% CI > -20 %.
Of the 4474 participants exposed to Supemtek in a phase 3 active-controlled study (PSC12), a total of 1761 were 65 years or older. The number of patients aged 65 and over in this study was not sufficient to determine statistically whether this age group will respond differently from younger individuals.

Table 3: Relative Vaccine Efficacy (rVE) of Supemtek versus Comparator against Laboratory-Confirmed Influenza, Regardless of Antigenic Similarity to Vaccine Antigens, Adults 50 Years of Age and Older, PSC12 (Efficacy Population)[1,2]

	Supemtek (N=4303)		Comparator (N=4301)		RR	rVE % (95% CI)
	n	Attack Rate % (n/N)	n	Attack Rate % (n/N)		

All rtPCR-positive Influenza[3]	96	2.2	138	3.2	0.70	30 (10^5, 47)
All rtPCR-positive Influenza A[3]	73	1.7	114	2.7	0.64	36 (14, 53)
All rtPCR-positive Influenza B[3]	23	0.5	24	0.6	0.96	4 (-72, 46)
All Culture-confirmed Protocol-defined ILI3,4	58	1.3	101	2.3	0.57	43 (21, 59)

Abbreviations: rtPCR=reverse transcriptase polymerase chain reaction; Comparator= an egg-based quadrivalent inactivated influenza vaccine; n=number of influenza cases; N=number of subjects in treatment group; RR=relative risk (Attack Rate Supemtek/Attack Rate IIV4); rVE = [(1-RR) x 100].

[1] Excluded subjects with protocol deviations that could adversely affect efficacy.

[2] Primary Analysis. All cases of rtPCR-confirmed influenza are included.

[3] *Post hoc* analyses. All cases of influenza A were A/H3N2. Cases of influenza B were not distinguished by lineage.

[4] Culture of rtPCR-positive samples was performed in MDCK cells.

[5] The lower bound (LB) of the 95 % confidence interval met the pre-specified, exploratory criterion for superior relative vaccine efficacy, LB > 9 %.

Efficacy of trivalent recombinant influenza vaccine (RIV3)

The efficacy of a trivalent recombinant influenza vaccine (RIV3) is relevant to Supemtek because similar process is used in the manufacture of both vaccines and the composition is overlapping.

The efficacy of trivalent recombinant influenza vaccine in protecting against influenza illness was evaluated in a randomized, observer-blind, placebo-controlled multicenter trial conducted in the United States during the 2007-2008 influenza season in adults 18-49 years of age (Study PSC04). Study PSC04 enrolled and vaccinated 4648 healthy adults randomized in a 1:1 ratio to receive a single dose of RIV3 (n=2344) or saline placebo (n=2304).

Culture-confirmed influenza was assessed by active and passive surveillance for influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 7 months post- vaccination.

The primary efficacy endpoint of PSC04 was defined as an influenza-like illness (ILI) with a positive culture for an influenza virus strain antigenically resembling a strain represented in RIV3. ILI is defined as fever of ≥100°F (37.8°C) orally measured, accompanied by cough, sore throat, or both, on the same or consecutive days. Attack rates and vaccine efficacy (VE), defined as the reduction in the influenza rate for RIV3 relative to placebo, were calculated for the total vaccinated cohort (n=4648). The pre-defined success criterion for the primary efficacy analysis was that the lower bound of the 95% confidence interval (CI) of VE should be at least 40 %.

Due to very small number of cultured confirmed influenza cases with matched strains, an exploratory analysis of VE of RIV3 against all strains, regardless of antigenic match, isolated from any subject with any ILI, not necessarily meeting ILI criteria was done, demonstrated an efficacy estimate of 44.8 % (95% CI 24.4, 60.0). See Table 4 for VE by case definition.

Table 4: Vaccine Efficacy Against Culture-Confirmed Influenza in Healthy Adults 18-49 Years of Age, Study PSC04*

Case definition	RIV3 (N=2344)		Saline Placebo (N=2304)		RIV3 Vaccine Efficacy[1] %	95% Confidence Interval
	Cases, n	Rate, %	Cases, n	Rate, %		
Positive culture with a strain represented in the vaccine						
CDC-ILI, all matched strains[2,3]	1	0.04	4	0.2	75.4	(-148.0, 99.5)
Any ILI, all matched strains[4,5]	2	0.1	6	0.3	67.2	(-83.2, 96.8)
Positive culture with any strain, regardless of match to the vaccine						
CDC-ILI, all strains[2,6]	44	1.9	78	3.4	44.6	(18.8, 62.6)
Sub-Type A	26	1.1	56	2.4	54.4	(26.1, 72.5)
Type B	18	0.8	23	1.0	23.1	(-49.0, 60.9)
Any ILI, all strains[4,6]	64	2.7	114	4.9	44.8	(24.4, 60.0)
Sub-Type A	41	1.7	79	3.4	49.0	(24.7, 65.9)
Type B	23	1.0	36	1.6	37.2	(-8.9, 64.5)

*In Study PSC04 (NCT00539981) vaccine efficacy analyses were conducted on the Total Vaccinated Cohort (all randomized subjects who received study vaccine according to the treatment actually received and who provided data). Vaccine efficacy (VE) = 1 minus the ratio of Supemtek/placebo infection rates.

[1] Determined under the assumption of Poisson event rates, according to Breslow and Day, 1987.

[2] Meets CDC influenza-like illness (CDC-ILI) defined as fever of ≥100ºF (37,8 °C) orally measured, accompanied by cough and/or sore throat, on the same day or on consecutive days.

[3] Primary endpoint of trial.

[4] All culture-confirmed cases are considered, regardless of whether they qualified as CDC-ILI.

[5] Secondary endpoint of trial.

[6] Exploratory endpoint of trial.

Pharmacokinetics

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

Non-clinical data on the trivalent formulation revealed no special hazard for humans based on conventional studies of repeat dose and local toxicity, reproductive and developmental (including teratogenicity) toxicity and safety pharmacology studies.The results of these studies with trivalent

recombinant influenza vaccine are relevant to Supemtek because both vaccines are manufactured using the same process and have overlapping compositions.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze. Discard if frozen.
Keep the syringe in the outer carton in order to protect the contents from light.

Instructions for handling

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

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

Authorisation number

68003

Packs

0.5 mL solution in a pre-filled syringe (Type I borosilicate glass) with plunger stopper (grey butyl rubber), without needle.

Pack size:
1 pre-filled syringe, without needle. (B)
5 pre-filled syringes, without needle. (B)
10 pre-filled syringes, without needle. (B)

1 pre-filled syringe, with separate needle. (B)
5 pre-filled syringes, with separate needle. (B)
10 pre-filled syringes, with separate needle. (B)

Marketing authorisation holder

sanofi-aventis (suisse) sa, 1214 Vernier

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