NEW ZEALAND DATA SHEET

1. PRODUCT NAME

AREXVY 120 micrograms powder and suspension for suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 mL) contains 120 micrograms of RSVPreF3[1] antigen adjuvanted with AS01$_E$[2].

[1] Respiratory syncytial virus (RSV) glycoprotein F stabilized in the pre-fusion conformation (RSVPreF3) produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

[2] The GlaxoSmithKline proprietary AS01$_E$ Adjuvant System is composed of the plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) (25 micrograms) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* (25 micrograms).

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.

The powder is white.

The suspension is an opalescent, colourless to pale brownish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AREXVY is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults 60 years of age and older.

Consideration should be given to official vaccine recommendations on the appropriate use.

4.2 Dose and method of administration

Dose

Consideration should be given to official vaccine recommendations for immunisation schedules.

AREXVY is administered as a single dose of 0.5 mL.

The need for revaccination has not been established.

Method of administration

AREXVY is for intramuscular injection only, preferably in the deltoid muscle.

The powder and suspension should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not reconstitute the vaccine.

For instructions on reconstitution of the medicinal product before administration, 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Hypersensitivity to the active substances or to any component of the vaccine (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

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

As with other vaccines, vaccination with AREXVY should be postponed in individuals suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Precautions for use

Do not administer the vaccine intravascularly or intradermally. No data are available on subcutaneous administration of AREXVY.

As with other vaccines administered intramuscularly, AREXVY should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these individuals.

Systemic immunosuppressive medications and immunodeficiency

Safety and immunogenicity data on AREXVY are not available for immunocompromised individuals. Patients receiving immunosuppresive treatment or patients with immunodeficiency may have a reduced immune response to AREXVY.

4.5 Interaction with other medicines and other forms of interaction

Use with other vaccines

AREXVY can be given concomitantly with inactivated unadjuvanted seasonal influenza vaccine (Flu Quadrivalent containing a combined total of 60 micrograms Hemagglutinin (HA) per dose) *(*see *Pharmacodynamic Effects)*.

Data are currently not available for concomitant administration with other vaccines.

If AREXVY is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of AREXVY in pregnant women. AREXVY is not recommended during pregnancy.

After administration of an investigational unadjuvanted RSVPreF3 vaccine to 3,557 pregnant women in a single clinical trial, an increase in preterm births was observed compared to placebo.

Breast-feeding

There are no data on the excretion of AREXVY in human or animal milk. AREXVY is not recommended in breast-feeding/lactating women.

Fertility

There are no data on the effects of AREXVY on human fertility. Effects on male or female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

No studies on the effects of AREXVY on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

The safety profile presented below is based on a placebo-controlled Phase III clinical study (conducted in Europe, North America, Asia and Southern hemisphere) in adults ≥ 60 years of age in which 12,467 adults received one dose of AREXVY and 12,499 received placebo.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000

Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	lymphadenopathy
Immune system disorders	Uncommon	hypersensitivity reactions (such as rash)
Nervous system disorders	Very common	headache
Respiratory, thoracic, and mediastinal disorders	Common	rhinorrhea
Gastrointestinal disorders	Uncommon	nausea, abdominal pain
Musculoskeletal and connective tissue disorders	Very common	myalgia, arthralgia
General disorders and administration site conditions	Very common	injection site pain, fatigue
	Common	injection site erythema, injection site swelling, fever, chills
	Uncommon	injection site pruritus
		pain, malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Insufficient data are available.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned; ATC code: Not yet assigned

Mechanism of action

The risk of developing RSV-associated LRTD increases with age and with presence of underlying comorbidities. AREXVY induces the functional humoral immune responses against the RSV-A and RSV-B subtypes and the antigen-specific cellular immune responses which contribute to protect against RSV-associated LRTD (see *Immunogenicity of AREXVY*).

In a Phase I/II clinical trial, formulation adjuvanted with $AS01_E$ showed the ability to restore RSVPreF3-specific CD4+ T cells in adults 60 to 80 years of age to levels similar to those observed in young adults, despite lower baseline levels in the older adults.

Non-clinical data show that $AS01_E$ induces a local and transient activation of the innate immune system through specific molecular pathways. The adjuvant effect of $AS01_E$ is the result of interactions between MPL and QS-21 formulated in liposomes. This facilitates the recruitment and activation of antigen presenting cells carrying vaccine-derived antigens in the draining lymph node, which in turn leads to the generation of RSVPreF3-specific CD4+ T cells and induction of RSV-A and RSV-B neutralizing antibody responses. In addition, RSVPreF3 formulated with $AS01_E$ can elicit specific binding antibodies directed to site Ø, a highly neutralizing sensitive epitope, exposed only on the pre-fusion conformation of the F protein.

Clinical efficacy and safety

<u>Efficacy of AREXVY</u>

Efficacy of AREXVY against RSV-associated LRTD in adults 60 years and older was evaluated in RSV OA=ADJ-006, an ongoing, Phase III, randomised, placebo-controlled, observer-blind clinical study conducted in 17 countries from Northern and Southern Hemispheres. Participants are planned to be followed for up to 36 months.

The primary population for efficacy analysis (referred to as the modified Exposed Set, included adults 60 years of age and older receiving 1 dose of AREXVY or placebo and who did not report an RSV-confirmed acute respiratory illness (ARI) prior to Day 15 after vaccination) included 24,960 participants randomised equally to receive 1 dose of AREXVY (N = 12,466) or placebo (N = 12,494). At the time of the primary efficacy analysis, participants had been followed for the development of RSV-associated LRTD for up to 10 months (median of 6.7 months).

At baseline, 39.3% of participants had at least one comorbidity of interest; 19.7% of participants had an underlying cardiorespiratory condition (COPD, asthma, any chronic respiratory/pulmonary disease, or chronic heart failure) and 25.8% of participants had endocrinometabolic conditions (diabetes, advanced liver or renal disease).

Using the Gait speed test, 38.3% of participants were ranked as pre-frail (0.4-0.99m/s walking speed) and 1.5% as frail (<0.4 m/s walking speed or who were not able to perform the test).

Efficacy against RSV-associated LRTD

The primary objective was to demonstrate the efficacy of AREXVY in the prevention of a first episode of confirmed RSV-A and/or B associated LRTD during the first season. Confirmed RSV cases were determined by quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) on nasopharyngeal swab. LRTD was defined based on the following criteria: the participant must have experienced at least 2 lower respiratory symptoms/signs including at least 1 lower respiratory sign for at least 24 hours, or experienced at least 3 lower respiratory symptoms for at least 24 hours. Lower respiratory symptoms included: new or increased sputum, new or increased cough, new or increased dyspnea (shortness of breath). Lower respiratory signs included: new or increased wheezing, crackles/ronchi, respiratory rate ≥ 20 respirations/min, low or decreased oxygen saturation (O_2 saturation <95% or ≤90 % if baseline is <95%) or need for oxygen supplementation.

Compared with placebo, AREXVY significantly reduced the risk of developing RSV-associated LRTD by 82.58% (96.95% CI: [57.89, 94.08]) in participants 60 years of age and older, which met the pre-specified success criterion for the primary study objective (Table 1). High vaccine efficacy against RSV-LRTD is observed through the median follow-up period of 6.7 months.

The vaccine efficacy against RSV A-associated LRTD cases and RSV B-associated LRTD cases was 84.62% (95% CI [32.08, 98.32]) and 80.88% (95% CI [49.40, 94.27]), respectively.

Table 1. Efficacy Analysis: First RSV-associated LRTD Overall, by Age and co-morbidity subgroups in RSV OA=ADJ-006 (modified Exposed Set)

Subgroup	AREXVY			Placebo			% Efficacy (CI)[a]
	N	n	Incidence Rate per 1,000 Person-Years	N	n	Incidence Rate per 1,000 Person-Years	
Overall (≥ 60 years)[b]	12466	7	1.0	12494	40	5.8	82.58 (57.89, 94.08)
60-69 years	6963	4	1.0	6979	21	5.5	80.96 (43.56, 95.25)
70-79 years	4487	1	0.4	4487	16	6.5	93.81 (60.15, 99.85)
Participants with at least 1 comorbidity of interest	4937	1	0.4	4861	18	6.6	94.61 (65.88, 99.87)

[a]CI = Confidence Interval (96.95% for the overall (≥ 60 years) and 95% for all subgroup analyses). Two-sided exact CI for vaccine efficacy is derived based on Poisson model adjusted by age categories and regions.

[b]Primary confirmatory objective with pre-specified success criterion of lower limit of the 2-sided CI for vaccine efficacy above 20%

N = Number of participants included in each group

n = Number of participants having first occurrence of RSV-confirmed LRTD occurring from Day 15 post vaccination

Compared with placebo, AREXVY significantly reduced the risk of developing RSV-associated LRTD by 84.37% (95% CI: [46.91, 97.04]) in participants 70 years of age and older. The vaccine efficacy in the subgroup of participants 80 years of age and older (1016 participants in AREXVY vs 1028 participants in placebo) cannot be concluded due to the low number of total cases accrued (5 cases).

Compared with placebo, AREXVY significantly reduced the risk of developing RSV-associated LRTD in pre-frail participants by 92.92% (95% CI [53.44, 99.83]). The vaccine efficacy in the frail subgroup (189 participants in AREXVY vs 177 participants in placebo) cannot be concluded due to the low number of total cases accrued (2 cases).

Efficacy Against Severe RSV-associated LRTD and RSV-associated ARI

In study RSV-OA=ADJ-006, severe RSV-associated LRTD was defined as RT-PCR confirmed RSV-associated LRTD with at least 2 lower respiratory signs, or as an RT-PCR confirmed RSV-associated LRTD episode assessed as ‘severe’ by the investigator. One case of severe RSV-associated LRTD in the AREXVY group and 17 cases in the placebo group were reported, amongst which 2 cases required supportive therapy. Compared with placebo, AREXVY significantly reduced the risk of developing severe RSV-associated LRTD by 94.10 % (95% CI [62.37, 99.86]) in participants 60 years of age and older.

Acute respiratory illness (ARI) was defined by the presence of at least 2 respiratory symptoms/signs for at least 24 hours, or at least 1 respiratory symptom/sign + 1 systemic symptom/sign (fever or feverishness, fatigue, body aches, headache, decreased appetite) for at least 24 hours. AREXVY significantly reduced the risk of developing confirmed RSV-associated ARI in adults ≥ 60 years of age by 71.71% (95% CI [56.23, 82.27]).

Patient Reported Outcome

AREXVY was assessed vs. placebo in the RSV OA=ADJ-006 study to quantify the reduction in intensity of respiratory symptoms using a patient reported outcome measure, the FLU-PRO questionnaire. In participants with an RSV-confirmed ARI episode who completed the FLU-PRO questionnaire, AREXVY significantly reduced the intensity of lower respiratory tract symptoms of RSV by a clinically meaningful difference vs. placebo as assessed by the maximum FLU-PRO Chest score (scale range 0-4) over the first 7 days of the episode (Mean [standard deviation] of 1.32 [1.02] in the AREXVY group vs 1.90 [0.93] in the placebo group).

Immunogenicity of AREXVY

An immunological correlate of protection has not been established, therefore, the level of immune response that provides protection against RSV-associated LRTD is unknown.

The immune responses to AREXVY were evaluated in a Phase III immunogenicity and safety study RSV OA=ADJ-004 in adults 60 years and older. Functional humoral immune responses post-vaccination compared to pre-vaccination were evaluated with results from 940 participants for RSV-A and 941 participants for RSV-B for month 1 vs. pre-vaccination, and 928 participants for RSV-A and 929 participants for RSV-B at month 6 vs. pre-vaccination. The cell-mediated immune responses were evaluated with results from 471 participants at pre-vaccination, 410 at month 1 and 440 at month 6.

AREXVY elicited RSV-specific humoral and cellular immune responses. The geometric mean increase of the RSV-A and RSV-B neutralizing titers compared to pre-vaccination were 10.5-fold (95% CI [9.9, 11.2]) and 7.8-fold (95% CI [7.4, 8.3]) at 1-month post-vaccination, respectively, and 4.4-fold (95% CI [4.2, 4.6]) and 3.5-fold (95% CI [3.4, 3.7]) at 6-months post-vaccination, respectively. The median frequency (percentile [25^{th}, 75^{th}]) of the RSVPreF3-specific CD4+ T-cells (per million of CD4+ T cells) was 1339.0 (829.0, 2136.0) 1-month post-vaccination and 666.0 (428.0, 1049.5) 6-months post-vaccination as compared to 191.0 (71.0, 365.0) pre-vaccination.

Immunogenicity following concomitant vaccination

In an open-label Phase III clinical study, participants 60 years of age and older received 1 dose of AREXVY and inactivated seasonal influenza vaccine (Flu Quadrivalent containing a combined total of 60 micrograms Hemagglutinin (HA) per dose) at month 0 (N = 442), or 1 dose of Flu Quadrivalent at month 0 followed by a dose of AREXVY at month 1 (N = 443).

There was no evidence for interference in the immune response to any of the antigens contained in both co-administered vaccines. The criteria for non-inferiority

of the immune responses in the control versus co-administration group were met as the 2-sided 95% confidence interval upper limits on the group geometric mean titer ratios were below 1.50 for the RSV-A neutralizing antibodies and haemagglutinin inhibition antibodies against the strains Flu A/Hong Kong/H3N2, Flu A/Victoria/H1N1, Flu B/Phuket/Yamagata, and Flu B/Washington/Victoria.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Genotoxicity

AREXVY was not tested for genotoxicity.

Carcinogenicity

AREXVY was not tested for carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder (RSVPreF3 antigen):

Trehalose dihydrate

Polysorbate 80

Monobasic potassium phosphate

Dibasic potassium phosphate

Suspension (AS01$_E$ Adjuvant System):

Dioleoyl phosphatidylcholine

Cholesterol

Sodium chloride

Dibasic sodium phosphate

Monobasic potassium phosphate

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze. Discard if the vial has been frozen.

Store in the original package in order to protect from light.

After reconstitution, the vaccine should be used promptly; if not possible, the vaccine should be stored in the refrigerator (2°C – 8°C) or at room temperature up to 25°C. If not used within 4 hours it should be discarded.

6.5 Nature and contents of container

Powder for 1 dose in a vial (type I glass) with stopper (butyl rubber).

Suspension for 1 dose in a vial (type I glass) with a stopper (butyl rubber).

AREXVY is available in a pack size of 1 vial of powder plus 1 vial of suspension or in a pack size of 10 vials of powder plus 10 vials of suspension.

Not all pack sizes and container types may be distributed in New Zealand.

6.6 Special precautions for disposal and other handling

The powder and suspension should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not reconstitute the vaccine.

How to prepare AREXVY:

AREXVY must be reconstituted prior to administration.

1. Withdraw the entire contents of the vial containing the suspension into a syringe.
2. Add the entire contents of the syringe into the vial containing the powder.
3. Gently swirl until the powder is completely dissolved.

The reconstituted vaccine is an opalescent, colourless to pale brownish liquid.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.

Before administration:

1. Withdraw 0.5 mL of the reconstituted vaccine into the syringe.
2. Change the needle so that you are using a new needle.
3. Administer the vaccine intramuscularly.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 04 April 2024.

10. DATE OF REVISION OF THE TEXT

02 May 2024

Summary table of changes:

Section changed	Summary of new information
4.8	Adverse event reporting updated to new URL
6.3	Shelf life updated from 24 to 36 months

Version 2.0