ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Arexvy powder and suspension for suspension for injection
Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:
RSVPreF3[1] antigen[2,3] 120 micrograms

[1] Respiratory Syncytial Virus recombinant glycoprotein F stabilised in the pre-fusion conformation = RSVPreF3
[2] RSVPreF3 produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology
[3] adjuvanted with $AS01_E$ containing:
plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) 25 micrograms
3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* 25 micrograms

For the full list of excipients, see section 6.1.

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 in:

- adults 60 years of age and older;
- adults 50 through 59 years of age who are at increased risk for RSV disease.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Arexvy is administered as a single dose of 0.5 mL.

The need for revaccination with a subsequent dose has not been established (see section 5.1).

Paediatric population

The safety and efficacy of Arexvy in children have not been established.

No data are available.

Method of administration

For intramuscular injection only, preferably in the deltoid muscle.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Prior to immunisation

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Vaccination 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.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with the vaccination process itself. It is important that precautions are in place to avoid injury from fainting.

Precautions for use

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

As with other intramuscular injections, Arexvy should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following intramuscular administration to these individuals.

Systemic immunosuppressive medicinal products and immunodeficiency

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

Excipients

This medicinal product contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially ‘potassium-free’.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Use with other vaccines

Arexvy may be administered concomitantly with inactivated seasonal influenza vaccines (standard dose unadjuvanted, high dose unadjuvanted, or standard dose adjuvanted).

Upon concomitant administration of Arexvy with seasonal influenza vaccines, numerically lower RSV A and B neutralising titres and numerically lower influenza A and B haemagglutination inhibition titres were observed as compared to the separate administration. This was not observed consistently across studies. The clinical relevance of these findings is unknown.

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

Concomitant administration of Arexvy with other vaccines than those listed above has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Arexvy in pregnant women. After administration of an investigational unadjuvanted RSVPreF3 vaccine to 3 557 pregnant women in a single clinical study, an increase in preterm births was observed compared to placebo. Currently no conclusion on a causal relationship between administration of unadjuvanted RSVPreF3 and preterm birth can be drawn. Results from animal studies with Arexvy or with an investigational unadjuvanted RSVPreF3 vaccine do not indicate direct or indirect harmful effects with respect to developmental and reproductive toxicity (see section 5.3). Arexvy is not recommended during pregnancy.

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. Animal studies with Arexvy or with an investigational unadjuvanted RSVPreF3 vaccine do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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.

Arexvy has a minor influence on the ability to drive and use machines. Some of the effects mentioned under section 4.8 “Undesirable effects” (e.g. fatigue) may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile presented in Table 1 is based on a pooled analysis of data generated in two placebo-controlled Phase III clinical studies (conducted in Europe, North America, Asia and Southern hemisphere) in adults ≥ 60, and 50 through 59 years of age, and on post-marketing experience.

In study participants 60 years of age and older (more than 12 000 adults received one dose of Arexvy and more than 12 000 received placebo, with a follow-up period of approximately 12 months), the most commonly reported adverse reactions were injection site pain (61%), fatigue (34%), myalgia (29%), headache (28%), and arthralgia (18%). These adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination.
Most other adverse reactions were uncommon and similarly reported between the study groups.

In study participants 50 through 59 years of age (769 participants, including 386 participants with pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease), a higher incidence of injection site pain (76%), fatigue (40%), myalgia (36%), headache (32%), and arthralgia (23%) was observed, compared with those 60 years of age and older (381 participants) in the same study. However, the duration and severity of these events were comparable across age groups in the study.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA system organ class and 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)
Not known	(Cannot be estimated from the available data)

Table 1 presents adverse reactions observed in clinical trials as well as adverse reactions which have been spontaneously reported during the post-marketing use of Arexvy worldwide.

Table 1. 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
Gastrointestinal disorders	Uncommon	nausea, abdominal pain, vomiting
Musculoskeletal and connective tissue disorders	Very common	myalgia, arthralgia
General disorders and administration site conditions	Very common	injection site pain, injection site erythema, fatigue
	Common	injection site swelling, fever, chills
	Uncommon	injection site pruritus
		pain, malaise
	Not known	injection site necrosis[1]

[1]Adverse reaction from spontaneous reporting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported in the clinical studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, other viral vaccines, ATC code: J07BX05.

Mechanism of action

By combining the RSV-specific antigen, F-protein in prefusion conformation, with an adjuvant system ($AS01_E$), Arexvy is designed to enhance antigen-specific cellular immune response and neutralizing antibodies response in individuals with pre-existing immunity against RSV. The adjuvant $AS01_E$

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.

Efficacy

Efficacy against RSV-associated LRTD in adults 60 years and older was evaluated in 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, defined as adults 60 years of age and older who received 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 first confirmatory efficacy analysis, participants had been followed for the development of RSV-associated LRTD for a median of 6.7 months.

The median age of participants was 69 years (range: 59 to 102 years), with approximately 74% over 65 years of age, approximately 44% over 70 years of age and approximately 8% over 80 years of age. Approximately 52% were female. 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).

Efficacy against RSV-associated LRTD during the first RSV season (confirmatory analysis)

The primary objective was to demonstrate efficacy in the prevention of a first episode of confirmed RSV-A and/or B associated LRTD during the first RSV 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 dyspnoea (shortness of breath). Lower respiratory signs included: new or increased wheezing, crackles/rhonchi, 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.

Vaccine efficacy overall and by subgroups is presented in Table 2.

Efficacy in preventing first RSV-associated LRTD with an onset from 15 days after vaccination compared to placebo was 82.6% (96.95% confidence interval of 57.9% to 94.1%) in participants 60 years of age and older. Vaccine efficacy against RSV-LRTD was observed through the median follow-up period of 6.7 months. Vaccine efficacy against RSV A-associated LRTD cases and RSV B-associated LRTD cases was 84.6% (95% CI [32.1, 98.3]) and 80.9% (95% CI [49.4, 94.3]), respectively.

Table 2. Efficacy analysis during the first RSV season (confirmatory analysis): First RSV-associated LRTD overall, by age and co-morbidity subgroups (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]	12 466	7	1.0	12 494	40	5.8	82.6 (57.9, 94.1)
60-69 years	6 963	4	1.0	6 979	21	5.5	81.0 (43.6, 95.3)
70-79 years	4 487	1	0.4	4 487	16	6.5	93.8 (60.2, 99.9)
Participants with at least 1 comorbidity of interest	4 937	1	0.4	4 861	18	6.6	94.6 (65.9, 99.9)

[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]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

Vaccine efficacy in the subgroup of participants 80 years of age and older (1 016 participants in Arexvy vs 1 028 participants in placebo) cannot be concluded due to the low number of total cases accrued (5 cases).

Amongst 18 RSV-LRTD cases with at least 2 lower respiratory signs or preventing everyday activities, 4 cases of severe RSV-LRTD requiring oxygen supplementation occurred in the placebo group compared to none in the Arexvy group.

Efficacy against RSV-associated LRTD over 2 RSV seasons

Over 2 RSV seasons (up to end of second season in Northern Hemisphere), with a median follow-up time of 17.8 months, vaccine efficacy against RSV-associated LRTD was 67.2% (97.5% CI [48.2, 80.0]) in participants 60 years of age and older (30 cases in the Arexvy group and 139 cases in the placebo group).

Vaccine efficacy against RSV-associated LRTD was similar in the subgroup of participants with at least one comorbidity of interest.

A second dose of vaccine administered 12 months after the first dose did not confer additional efficacy benefit.

Immunogenicity in adults 50 through 59 years of age at increased risk for RSV disease

The non-inferiority of the immune response to Arexvy in adults 50 through 59 years of age compared to adults 60 years of age and older, where vaccine efficacy against RSV-associated LRTD was demonstrated, was evaluated in a Phase III, observer-blind, randomised, placebo-controlled study.

Cohort 1 consisted of participants 50 through 59 years of age separated in 2 sub-cohorts (Adults-AIR and Adults-non-AIR) according to their medical history. Adults-AIR (adults at increased risk) sub-cohort consisted of participants with pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease (Arexvy, N= 386; placebo, N= 191) such as chronic pulmonary disease, chronic cardiovascular disease, diabetes, chronic kidney or liver disease. Adults-non-AIR sub-cohort consisted of participants without pre-defined, stable, chronic medical conditions (Arexvy, N= 383; placebo, N= 192). Cohort 2 (OA; older adults) consisted of participants 60 years of age and older (Arexvy, N= 381).

The primary immunogenicity objectives were to demonstrate non-inferiority of the humoral immune response (in terms of RSV-A and RSV-B neutralising titers) following the administration of Arexvy at 1-month post-vaccination in participants 50 through 59 years of age with and without pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease, compared to participants 60 years of age and older.

Table 3. Summary of adjusted GMT and SRR values, and adjusted GMT ratios and SRR differences in terms of RSV-A and RSV-B neutralising titers (ED60) in adults 60 years of age and older (OA) relative to adults 50 through 59 years of age with (Adults-AIR) and without (Adults-non-AIR) pre-defined, stable, chronic medical conditions[a] leading to an increased risk for RSV disease – Per Protocol Set

RSV-A neutralising titers (ED60)				
	Adjusted GMT (95% CI)	**Adjusted GMT ratio (95% CI)** [b]	**SRR (%) (95% CI)**	**SRR difference (95% CI)** [c]
OA	7 440.1 (6 768.4, 8 178.5)	0.8 (0.7, 1.0)	80.4 (75.8, 84.5)	-6.5 (-12.1, -0.9)
Adults-AIR	8 922.7 (8 118.2, 9 806.9)		86.9 (82.8, 90.3)	
OA	7 492.6 (6 819.1, 8 232.7)	1.0 (0.8, 1.1)	80.4 (75.8, 84.5)	-2.4 (-8.3, 3.5)
Adults-non-AIR	7 893.5 (7 167.5, 8 692.9)		82.8 (78.3, 86.8)	
RSV-B neutralising titers (ED60)				
	Adjusted GMT (95% CI)	**Adjusted GMT ratio**[b]	**SRR (95% CI)**	**SRR difference** [c]
OA	8 062.8 (7 395.9, 8 789.9)	0.8 (95% CI [0.7, 0.9])	74.5 (69.5, 79.0)	-7.2 (95% CI [-13.3, -0.9])
Adults-AIR	10 054.7 (9 225.4, 10 958.7)		81.6 (77.1, 85.6)	
OA	8 058.2 (7 373.1, 8 807.0)	0.9 (97.5% CI [0.8, 1.0])	74.5 (69.5, 79.0)	-3.7 (97.5% CI [-11.1, 3.7])
Adults-non-AIR	9 009.5 (8 226.8, 9 866.6)		78.2 (73.3, 82.6)	

[a] Pre-defined, stable, chronic medical conditions such as chronic pulmonary disease, chronic cardiovascular disease, diabetes, chronic kidney or liver disease.

[b,c] The prespecified criteria for non-inferiority of the immune responses were defined as the 2-sided 95% or 97.5% CI upper limits (UL) on the adjusted GMT ratios (OA over Adults-AIR or Adults-non-AIR) ≤ 1.5 and the UL of the 2-sided 95% or 97.5% CI on the SRR difference (OA minus Adults-AIR or Adults-non-AIR) ≤ 10% in participants 60 years of age and older (OA) relative to participants 50 through 59 years of age with (Adults-AIR) or without (Adults-non-AIR) pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease

ED60: Estimated dilution 60; CI = Confidence interval; GMT = Geometric mean titer; SRR = Seroresponse rate

The non-inferiority criteria of the immune responses for the RSV-A and RSV-B neutralising titers were met. The efficacy of Arexvy, in adults 50 through 59 years of age at increased risk for RSV disease, can be inferred following comparison of the immune response in adults 50 through 59 years of age with the immune response in adults 60 years of age and older in whom vaccine efficacy was demonstrated.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Arexvy in one or more subsets of the paediatric population in prevention of lower respiratory tract disease caused by respiratory syncytial virus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.
Reproductive and developmental studies in rabbits with Arexvy or with an unadjuvanted RSVPreF3 vaccine did not reveal vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder (RSVPreF3 antigen)

Trehalose dihydrate
Polysorbate 80 (E 433)
Potassium dihydrogen phosphate (E 340)
Dipotassium phosphate (E 340)

Suspension (AS01E Adjuvant System)

Dioleoyl phosphatidylcholine (E 322)
Cholesterol
Sodium chloride
Disodium phosphate, anhydrous (E 339)
Potassium dihydrogen phosphate (E 340)
Water for injections

For adjuvant see also section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution

Chemical and physical in-use stability has been demonstrated for 4 hours at 2 °C – 8 °C or at room temperature up to 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 4 hours.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Arexvy is presented as:

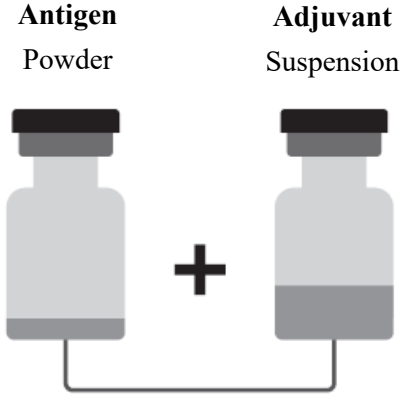
- Powder for 1 dose in a vial (type I glass) with a stopper (butyl rubber) and a mustard green flip-off cap (antigen).
- Suspension for 1 dose in a vial (type I glass) with a stopper (butyl rubber) and a brown flip-off cap (adjuvant).

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 may be marketed.

6.6 Special precautions for disposal and other handling

The powder and the suspension must be reconstituted prior to administration.



1 dose (0.5 mL)

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.

Chemical and physical in-use stability has been demonstrated for 4 hours at 2 °C – 8 °C or at room temperature up to 25 °C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 4 hours.

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.

Administer the vaccine intramuscularly.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1740/001
EU/1/23/1740/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 June 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

GlaxoSmithKline Biologicals SA
Avenue Fleming, 20
1300 Wavre
Belgium

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals SA
Rue de L'Institut 89
1330 Rixensart
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Arexvy powder and suspension for suspension for injection
Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 mL) contains 120 micrograms of Respiratory Syncytial Virus recombinant glycoprotein F stabilised in the pre-fusion conformation adjuvanted with $AS01_E$

3. LIST OF EXCIPIENTS

Powder:
Trehalose dihydrate, Polysorbate 80, Potassium dihydrogen phosphate, Dipotassium phosphate.

Suspension:
Dioleoyl phosphatidylcholine, Cholesterol, Sodium chloride, Disodium phosphate, anhydrous, Potassium dihydrogen phosphate, Water for injections.

See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and suspension for suspension for injection
1 vial: powder (antigen)
1 vial: suspension (adjuvant)

10 vials: powder (antigen)
10 vials: suspension (adjuvant)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Powder and suspension to be reconstituted before administration

Antigen **Adjuvant**

1 dose (0.5 mL)

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1740/001 1 vial and 1 vial
EU/1/23/1740/002 10 vials and 10 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Antigen for Arexvy
IM

2. METHOD OF ADMINISTRATION

Mix with adjuvant

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Adjuvant for Arexvy

2. METHOD OF ADMINISTRATION

Mix with antigen

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 mL)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Arexvy powder and suspension for suspension for injection
Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Arexvy is and what it is used for

Arexvy is a vaccine that helps to protect adults aged 60 years and older against a virus called 'respiratory syncytial virus' (RSV).

Arexvy also helps to protect against RSV in adults 50 through 59 years of age at increased risk for RSV disease.

RSV is a respiratory virus that spreads very easily.
- RSV can cause lower respiratory tract disease - infections of the lungs and other parts of the body that help you breathe.

RSV infection usually causes mild, cold-like signs in healthy adults. But it can also:
- cause more serious respiratory illnesses and complications, such as infections of the lungs (pneumonia), in older adults and adults with underlying medical conditions
- make some illnesses worse, such as long-term respiratory or heart diseases.

How Arexvy works

Arexvy helps your body's natural defences make antibodies and special white blood cells. These protect you against RSV.

Arexvy does not contain the virus. This means it cannot cause an infection.

2. What you need to know before you receive Arexvy

Do not use Arexvy

- if you are allergic to the active substances or any of the other ingredients of this vaccine

(listed in section 6).
Do not use Arexvy if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you receive Arexvy if:

- you have ever had a severe allergic reaction after the injection of any other vaccine
- you have a severe infection with a high temperature (fever). If this happens, the vaccination may be delayed until you feel better. A minor infection such as a cold should not be a problem but talk to your doctor first
- you have a bleeding problem or bruise easily
- you have fainted with a previous injection - fainting can happen before or after any needle injection.

If any of the above apply to you, or you are not sure, talk to your doctor or pharmacist before you have Arexvy.

As with all vaccines, Arexvy may not fully protect all people who are vaccinated.

Other medicines/vaccines and Arexvy

Tell your doctor or pharmacist if:

- you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.
- you have recently received any other vaccine.

Arexvy may be given at the same time as a flu vaccine.

If Arexvy is given at the same time as another injectable vaccine, a different injection site will be used for each vaccine, which means a different arm for each injection.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this vaccine.
Arexvy is not recommended during pregnancy or breast-feeding.

Driving and using machines

Some of the effects mentioned below in section 4 “Possible side effects” (e.g. feeling tired) may temporarily affect the ability to drive or use machines. Do not drive or use machines or tools if you are feeling unwell.

Arexvy contains sodium and potassium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

This medicine contains less than 1 mmol (39 mg) potassium per dose, i.e. essentially ‘potassium-free’.

3. How Arexvy is given

Arexvy is given as a single dose injection of 0.5 mL into a muscle. It is usually given into the upper arm.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects may happen after receiving Arexvy:

Very common (these may occur with more than 1 in 10 doses of the vaccine):
- pain at the injection site
- feeling tired (fatigue)
- headache
- muscle pain (myalgia)
- joint pain (arthralgia)
- redness where the injection is given

Common (these may occur with up to 1 in 10 doses of the vaccine):
- swelling where the injection is given
- fever
- chills

Uncommon (these may occur with up to 1 in 100 doses of vaccine):
- itching at the injection site
- pain
- generally feeling unwell (malaise)
- enlarged lymph nodes, or swollen glands in the neck, armpit or groin (lymphadenopathy)
- allergic reactions such as rash
- feeling sick (nausea)
- vomiting
- stomach pain

Not known (cannot be estimated from the available data):
- death of skin tissue in the injection site (injection site necrosis)

Tell your doctor or pharmacist if you get any of the side effects listed above. Most of these side effects are mild to moderate in intensity and do not last long.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Arexvy

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C – 8 °C).
- Do not freeze.
- Store in the original package in order to protect from light.

- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Arexvy contains

- The active substances are:

  After reconstitution, one dose (0.5 mL) contains:

  RSVPreF3[1] antigen[2,3]
  120 micrograms

  [1] Respiratory Syncytial Virus recombinant glycoprotein F stabilised in the pre-fusion conformation = RSVPreF3

  [2] RSVPreF3 produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

  [3] adjuvanted with $AS01_E$ containing:
  plant extract Quillaja saponaria Molina, fraction 21 (QS-21) 25 micrograms
  3-O-desacyl-4'-monophosphoryl lipid A (MPL) from Salmonella minnesota 25 micrograms

  The RSVPreF3 is a protein present in the Respiratory Syncytial Virus. This protein is not infectious.

  The adjuvant is used to improve the body's response to the vaccine.

- The other ingredients are:
  - **Powder** (RSVPreF3 antigen): Trehalose dihydrate, polysorbate 80 (E 433), potassium dihydrogen phosphate (E 340), dipotassium phosphate (E 340).
  - **Suspension**: Dioleoyl phosphatidylcholine (E 322), cholesterol, sodium chloride, disodium phosphate anhydrous (E 339), potassium dihydrogen phosphate (E 340) and water for injections.

  See Section 2 "Arexvy contains sodium and potassium".

What Arexvy looks like and contents of the pack

- Powder and suspension for suspension for injection.
- The powder is white.
- The suspension is an opalescent, colourless to pale brownish liquid.

One pack of Arexvy consists of:
- Powder (antigen) for 1 dose in a vial
- Suspension (adjuvant) for 1 dose in a vial

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 may be marketed.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals SA

Rue de l'Institut 89
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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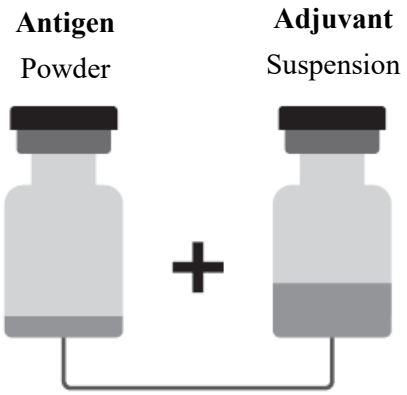
The following information is intended for healthcare professionals only:

Arexvy is presented as a vial with a mustard green flip-off cap containing the powder (antigen) and a vial with a brown flip-off cap containing the suspension (adjuvant).

The powder and the suspension must be reconstituted prior to administration.



1 dose (0.5 mL)

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 the 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.

Chemical and physical in-use stability has been demonstrated for 4 hours at 2 °C – 8 °C or at room temperature up to 25 °C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 4 hours.

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.

Administer the vaccine intramuscularly.

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

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for respiratory syncytial virus, glycoprotein f, recombinant, stabilised in the pre-fusion conformation, adjuvanted with as01e, the scientific conclusions of PRAC are as follows:

In view of available data on injection site necrosis from spontaneous reports, including at least 7 cases with a close temporal relationship, and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between respiratory syncytial virus, glycoprotein f, recombinant, stabilised in the pre-fusion conformation, adjuvanted with as01e and injection site necrosis is at least a reasonable possibility. The PRAC concludes that the product information of products containing 'respiratory syncytial virus, glycoprotein f, recombinant, stabilised in the pre-fusion conformation, adjuvanted with as01e' should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for respiratory syncytial virus, glycoprotein f, recombinant, stabilised in the pre-fusion conformation, adjuvanted with as01e the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing respiratory syncytial virus, glycoprotein f, recombinant, stabilised in the pre-fusion conformation, adjuvanted with as01e is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

In addition, the CHMP has the following comments on the PRAC assessment report:

CHMP notes that the mechanism or risk factors for the occurrence of "injection site necrosis" following vaccination with respiratory syncytial virus, glycoprotein f, recombinant, stabilised in the pre-fusion conformation, adjuvanted with as01e remain uncertain: the event could be vaccine, antigen, adjuvant or procedure related. This, however, does not impact the conclusion of the PRAC, which CHMP confirms. Additionally, editorial amendments to section 4.8 of the SmPC have been introduced to integrate the requested updates. This has been agreed by the CHMP.