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

SIILTIBCY (0.5 microgram + 0.5 microgram)/mL solution for injection
Mycobacterium tuberculosis derived antigens (rdESAT-6 and rCFP-10)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.1 mL) contains 0.05 microgram of rdESAT-6* and 0.05 microgram of rCFP-10**.

*Recombinant dimer of *Mycobacterium tuberculosis* early secretory antigenic target[1]
**Recombinant culture filtrate protein of *Mycobacterium tuberculosis*[1]

[1]Produced in *Lactococcus lactis* cells

Multidose vial.

One vial (1 mL) contains 10 doses of 0.1 mL.

Excipient with known effect

Each dose (0.1 mL) contains 0.011 mg of polysorbate 20.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless to pale-yellow solution, with a pH of 7.2 – 7.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SIILTIBCY is indicated as a diagnostic aid for detection of *Mycobacterium tuberculosis* infection, including disease, in adults and children aged 28 days or older.

This medicinal product is for diagnostic use only.

4.2 Posology and method of administration

Posology

The dose is 0.1 mL of SIILTIBCY.

Special populations

Elderly

There is only limited data on the safety and efficacy for SIILTIBCY in individuals aged 65 years and above. No dose adjustment is necessary for this population.

Paediatric population

The safety and efficacy of SIILTIBCY in newborn infants aged under 28 days have not been established. No data are available.

Method of administration

SIILTIBCY should be prepared and administered via intradermal injection by healthcare professionals trained for the Mantoux technique. The medicinal product should be administered with adequate hygiene of the hands and using aseptic technique, as follows:

- Withdraw 0.1 mL of SIILTIBCY using a 1 mL syringe with a short-bevel needle. Before drawing SIILTIBCY from the multidose vial, expel any air from the syringe. If the vial was already opened, swab it with an alcohol swab and let it dry before use.
- Administer the 0.1 mL of SIILTIBCY intradermally in the middle-third of the forearm using the Mantoux technique. Therefore, stretch the skin slightly and hold the needle almost parallel to the skin surface with the bevel upwards. Insert the tip of the needle into the superficial layer of the dermis. Make sure the needle is visible through the epidermis during the injection. Do not apply the test in areas of scars, rashes, burn or tattoos.
- Inject the drawn 0.1 mL solution slowly. A small-blanched papule of 8-10 millimetres (mm) in diameter will appear, which should disappear after about 10 minutes. If the papule does not appear, repeat a new injection of 0.1 mL of SIILTIBCY on the other arm or on the same arm at least 4 cm away from the first injection site.

Evaluating the reaction

Intradermal injected SIILTIBCY may induce an induration at the site of injection. The induration can be seen as a raised area with clearly defined margin at and around the injection site. Although erythema can accompany the induration, only the induration should be measured.

The induration is measured 48 to 72 hours after the injection by a trained healthcare professional. Measure the diameter of the induration transversely to the long axis of the forearm with a ruler. To allow ease with measurement, a flexible (or easily bendable) ruler is suggested.

Normally the induration and erythema will decrease after 4 days and disappear within 28 days after the injection.

Interpretation

An induration of ≥ 5 mm is considered as a positive test result, which indicates infection with *Mycobacterium tuberculosis*.

Interpretation of skin test results should consider the specific context of use and risk assessment, and could be complemented by radiography and other diagnostic evaluations.

Performing a test before 6 to 8 weeks from *Mycobacterium tuberculosis* exposure might result in a false-negative result.

The risk of false-positive test results may increase if SIILTIBCY is repeated within 6 weeks. Therefore, an interval of at least 6 weeks should be observed between repeated tuberculosis skin tests. This may be relevant for individuals taking part in a screening program such as healthcare professionals and contacts to active tuberculosis cases (i.e. index case).

As any diagnostic tool, false-negative results are possible (see section 5.1 for details). If a negative test result is found, but clinical suspicion is high, further examinations should be performed.

The test results are not influenced by previous vaccination with Bacillus Calmette-Guérin (BCG).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Hypersensitivity to *Lactococcus lactis*.
Severe local or systemic reaction to other *Mycobacterium tuberculosis* derived products.

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.

General recommendations

Anaphylaxis

Anaphylactic or other allergic type reactions are possible following administration of SIILTIBCY. Appropriate equipment for management of such reactions should always be available during the conduct of the test. Close observation for at least 15 minutes is recommended following the test.

Route of administration

Adherence to the Mantoux technique when administering SIILTIBCY is essential for obtaining reliable results, therefore avoid subcutaneous or intramuscular injection.

Special populations

The reactivity to SIILTIBCY can be lower or give false-negative results in immunocompromised individuals, including those receiving immunosuppressant therapy and human immunodeficiency virus (HIV) positive individuals if cluster of differentiation 4 positive (CD4+) thymus cell (T-cell) count is < 100 T-cells/mm^3. A positive test result indicates infection with *Mycobacterium tuberculosis* regardless of the CD4+ T-cell count.

There may be an increased risk of false-negative results in the elderly population due to immunosenescence with age.

Previous exposure to non-tuberculous mycobacteria

SIILTIBCY does not identify subjects with previous exposure to non-tuberculous mycobacteria as well as those who received Bacillus Calmette-Guérin vaccine or therapy, and thus use for this purpose is not appropriate.

Diagnosis of active tuberculosis

SIILTIBCY cannot be used as stand-alone tool for diagnosis of active tuberculosis disease. In addition, risk assessment, radiography, and other diagnostic evaluations should be considered for subjects suspected to have active tuberculosis.

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'.

This medicinal product contains 0.011 mg of polysorbate 20 in each dose, which is equivalent to 0.11 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Similar to other *Mycobacterium tuberculosis* skin tests, reactivity to SIILTIBCY may be decreased in persons who are receiving corticosteroids or immunosuppressive agents.

Reduced reactivity may be observed when SIILTIBCY is used after vaccination with live vaccines (e.g. vaccines against measles, mumps and rubella). This decreased reactivity may result in false-negative reactions. Therefore, SIILTIBCY should be administered either before or at the same time of the vaccination or should be postponed for 4 weeks after vaccination.

Regardless of the concomitant use of other medicinal products a positive test result indicates infection with *Mycobacterium tuberculosis*.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of SIILTIBCY in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

No effects during pregnancy are anticipated, since systemic exposure to SIILTIBCY is negligible. SIILTIBCY can be used during pregnancy.

Breast-feeding

No effects on the breast-fed newborns/infants are anticipated since the systemic exposure of the breast-feeding mother to SIILTIBCY is negligible. The skin test can be carried out during breast-feeding.

Fertility

No animal studies have been conducted on the effects of SIILTIBCY on fertility. Considering the negligible human systemic exposure to SIILTIBCY, no effects on fertility in male and female subjects is anticipated.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety profile presented below is based on data obtained from 7 clinical trials (TESEC-01 to TESEC-07), where SIILTIBCY was administered to 2 960 subjects (aged 32 days to 76 years) (Table 1).

The most common adverse reactions were injection site pruritus (20%), injection site pain (8%) and injection site hematoma (6%).

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following 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) and not known (cannot be estimated from the available data). Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported with SIILTIBCY (infants, children, adolescents and adults combined)

System organ class	**Frequency category**	**Adverse reactions**
Infections and infestations	Uncommon	Gastroenteritis
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy
	Rare	Lymphadenitis
		Eosinophilia
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Rare	Head discomfort
		Paraesthesia
Gastrointestinal disorders	Uncommon	Diarrhoea
		Nausea
	Rare	Vomiting
Hepatobiliary disorders	Rare	Hepatitis
		Jaundice
		Transaminases increased
Skin and subcutaneous tissue disorders	Uncommon	Rash
		Pruritus
	Rare	Night sweats
		Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Pain in extremity
	Rare	Myalgia
		Arthritis
General disorders and administration site conditions	Very common	Injection site pruritus
	Common	Injection site haematoma
		Injection site vesicles
		Injection site induration[#]
		Injection site swelling
		Injection site pain
		Injection site rash
		Injection site erythema
	Uncommon	Injection site ulcer

System organ class	Frequency category	Adverse reactions
		Injection site haemorrhage
		Pyrexia
		Malaise
		Fatigue
		Injection site discolouration
		Pain
		Influenza-like illness
	Rare	Axillary pain
		Injection site inflammation
		Injection site urticaria
		Injection site nodule
		Injection site papule
		Chills
		Injection site hypoaesthesia

#: Please refer to "Description of selected adverse reactions" for further details.

Description of selected adverse reactions

Injection site reactions

Mild injection site reactions were common and included pruritus, pain, haematoma, rash, vesicles, induration, erythema and swelling. Induration and erythema are expected reactions in individuals infected with *Mycobacterium tuberculosis.* Cases with induration more than 50 mm and erythema more than 80 mm are uncommon. Injection site reactions were generally transient and normally decreased in severity within 4 days and disappeared within 28 days.

Special population

Patients with HIV positive status at the time of screening visit were included in the clinical trials with SIILTIBCY if they were receiving antiretroviral therapy but were excluded if diagnosed with acquired immune deficiency syndrome (AIDS). Based on available data, frequency, type and severity of adverse reactions in the HIV positive status population seemed overall similar as in the general adult population.

Paediatric population

The safety assessment in children and adolescents is based on data obtained from 2 Phase 3 trials, TESEC-05 and TESEC-06, in which a total of 723 paediatric subjects aged from 32 days to 17 years received SIILTIBCY (see section 5.1). Overall, the safety profile in infants, children and adolescents was similar to that observed in the adult population.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned.

Mechanism of action

SIILTIBCY contains two recombinant *Mycobacterium tuberculosis* specific antigens, rdESAT-6 and rCFP-10. In case of infection with *Mycobacterium tuberculosis,* SIILTIBCY induces a delayed -type hypersensitivity reaction directed by cytokines, which are released by thymus helper cells type 1 after stimulation by the specific antigens included in SIILTIBCY.

This reaction is seen as an induration at the site of injection. The induration reaches its maximum 48 to 72 hours after administration.

Clinical efficacy

The diagnostic performance of SIILTIBCY to identify individuals infected with *Mycobacterium tuberculosis* was evaluated in 3 pivotal clinical trials TESEC-05, TESEC-06 and TESEC-07 (Table 2, Table 3) in comparison to other approved diagnostic immunological tuberculosis tests, i.e. the tuberculin purified protein derivative from the Statens Serum Institut (SSI) (PPD RT 23 SSI, herein after referred to as PPD) and QuantiFERON®-TB Gold in-Tube (QFT).

The sensitivity and specificity comparison of SIILTIBCY and other diagnostic tests (QFT and PPD) were evaluated in a *post hoc* analysis on the full analysis set (FAS) population with confirmed tuberculosis and in the negative control group, respectively (Table 2 and Table 3).

TESEC-05

This Phase 3 trial compared the diagnostic performance of SIILTIBCY *vs* QFT, in combination with a double-blind, randomised, split-body assessment of SIILTIBCY *vs* PPD. The primary trial objectives were to evaluate the performance of SIILTIBCY in relation to age, HIV status and CD4+ count, and to evaluate the clinical safety of SIILTIBCY, with an emphasis on children and HIV positive individuals. The primary endpoint was the test positivity rate for SIILTIBCY; secondary endpoints were comparisons of SIILTIBCY, PPD and QFT test positivity as well as sensitivity and specificity.

The trial was conducted in South Africa where tuberculosis is endemic, HIV infection prevalence is high and BCG vaccination at birth is routine practice.

A total of 1 190 subjects were enrolled of which 1 090 were suspected tuberculosis cases (0 to 65 years). Two hundred and ninety-nine subjects (25.1%) were HIV positive and 882 (74.1%) were BCG-vaccinated. The mean (standard deviation [SD]) age of all subjects was 22.5 (18.3) years with a range from 1 month to 65 years. The gender distribution was close to 50% (females 49.5% *vs* males 50.5%). The negative control population (n = 100) comprised of children aged 5 to 11 years old with no known contact with people infected with *Mycobacterium tuberculosis* and no signs of symptoms of tuberculosis.

Subjects were randomised to receive dual injections of SIILTIBCY and PPD in either forearm (split-body); blood samples for QFT analysis were collected prior to the administration of the skin tests, and test positivity rates were compared.

TESEC-06

This double-blind, randomised, split-body, Phase 3 trial conducted across 13 centres in Spain compared the diagnostic performance of SIILTIBCY with QFT in 4 risk groups (negative control, occasional contacts, close contacts, and positive controls). The primary objective was to assess whether a trend in SIILTIBCY test positivity would be seen with an increasing risk of *Mycobacterium tuberculosis* infection (i.e. from negative controls to the occasional contacts to close contacts). Secondary outcomes were comparisons of SIILTIBCY, QFT, and PPD test positivity, sensitivity and specificity.

Nine hundred and seventy-nine eligible subjects (aged 0 to 76 years) were enrolled, comprising 263 negative controls, 299 occasional contacts, 316 close contacts and 101 tuberculosis patients. The mean (SD) age of all enrolled subjects was 30.6 (14.5) years. Overall, 53.5% of the subjects were female and 46.5% male. Of all the enrolled subjects 366 (37.4%) were BCG-vaccinated. All subjects in the occasional and close contacts, and positive control groups, received dual injections of SIILTIBCY and PPD. In the negative control group, 213 subjects received dual injections of SIILTIBCY and PPD in different arms and a subgroup of 50 subjects received only SIILTIBCY in order to explore whether SIILTIBCY responses were affected by the concurrent administration of PPD. QFT testing was planned for all subjects aged 5 years and older, prior to the administration of the skin tests in order to avoid possible booster responses.

TESEC-07

This was a double-blind, randomised, controlled, Phase 2/3 clinical trial in adults with newly diagnosed, active pulmonary tuberculosis (PTB) and in treatment for < 2 weeks, conducted at 7 centres in South Africa. The primary trial objectives were to investigate and compare the induration sizes of SIILTIBCY and PPD when injected alone or concomitantly in different arms, and to assess if concomitant injections of SIILTIBCY and PPD influence the tests' sensitivity. Secondary trial objective was to compare the test positivity rates (sensitivity) of SIILTIBCY to that of PPD and QFT.

Four hundred and fifty-six eligible adults (aged 18 to 67 years) were enrolled and randomised into 1 of 3 treatment groups to receive either SIILTIBCY (n = 1534), PPD (n = 149) or SIILTIBCY and PPD (n = 153) in either forearm. Samples for QFT testing were collected prior to the administration of the skin tests.

In the FAS population, the mean age (SD) was 37.2 (12.7) years in the SIILTIBCY group, 36.3 (11.8) years for PPD and 35.3 (11.5) years for the SIILTIBCY and PPD group. Overall, 64.3% of the subjects were male and 35.7% female.

Table 2: Sensitivity analysis – individual clinical trials TESEC-05/-06/-07 (FAS populations with confirmed tuberculosis)

	SIILTIBCY		**QFT**		**PPD**		**Difference in sensitivity,% (95% CI)**	
Clinical trial	**n**	**Sensitivity, % (95% CI)**	**n**	**Sensitivity, % (95% CI)**	**n**	**Sensitivity, % (95% CI)**	**SIILTIBCY - QFT**	**SIILTIBCY - PPD**
TESEC-05	75	72.0 (61.8; 82.2)	70	58.6 (47.0; 70.1)	75	77.3 (67.9; 86.8)	13.4 (-3.3; 30.2)	-5.3 (-20.6; 9.9)
TESEC-06	100	68.0 (58.9; 77.1)	101	81.2 (73.6; 88.8)	100	81.0 (73.3; 88.7)	-13.2 (-26.1; -0.3)	-13.0 (-25.9; -0.1)
TESEC-07	305	78.0 (73.4; 82.7)	446	69.5 (65.2; 73.8)	303	87.1 (83.4; 90.9)	8.5 (1.9; 15.1)	-9.1 (-15.4; -2.8)

Abbreviations: BCG = Bacillus Calmette-Guérin; CI = confidence interval; FAS = full analysis set; HIV = human immunodeficiency virus; mm = millimetre; n = number of subjects in the population

with a test result; PPD = tuberculin purified protein derivative RT 23 SSI; QFT = QuantiFeron®-TB Gold in-Tube Test. Sensitivity analysis was performed *post hoc*. Percentages were calculated using n as the denominator. SIILTIBCY test diagnostic outcome used a cut-off point of ≥ 5 mm. PPD test diagnostic outcome used a test cut-off of ≥ 15 mm for HIV negative and BCG-vaccinated subjects and 5 mm otherwise. QFT test diagnostic outcome was based on manufacturer's algorithm. The QFT indeterminates were incorporated in the analysis as either "not positive" or "not negative" depending if sensitivity or specificity of QFT was calculated, respectively. Subjects with suspected tuberculosis were not considered in calculations of sensitivity.

Table 3: Specificity analysis – individual clinical trials TESEC-05/-06 (FAS populations with no tuberculosis)

	SIILTIBCY		QFT		PPD		Difference in specificity, % (95% CI)	
Clinical trial	**n**	**Specificity, % (95% CI)**	**n**	**Specificity, % (95% CI)**	**n**	**Specificity, % (95% CI)**	**SIILTIBCY - QFT**	**SIILTIBCY - PPD**
TESEC-05	100	83.0 (75.6; 90.4)	98	71.4 (62.5; 80.4)	100	85.0 (78.0; 92.0)	11.6 (-1.0; 24.2)	-2.0 (-13.2; 9.2)
TESEC-06	263	96.6 (94.4; 98.8)	263	96.2 (93.9; 98.5)	213	93.4 (90.1; 96.8)	0.4 (-3.2; 3.9)	3.2 (-1.3; 7.6)

Abbreviations: BCG = Bacillus Calmette-Guérin; CI = confidence interval; FAS = full analysis set; HIV = human immunodeficiency virus; mm = millimetre; n = number of subjects in the population with a test result; PPD = tuberculin purified protein derivative RT 23 SSI; QFT = QuantiFeron®-TB Gold in-Tube Test. Specificity analysis was performed *post hoc*. Percentages were calculated using n as the denominator. SIILTIBCY test diagnostic outcome used a cut-off of ≥ 5 mm. PPD test diagnostic outcome used a test cut-off of ≥ 15 mm for HIV negative and BCG-vaccinated subjects and 5 mm otherwise. QFT test diagnostic outcome was based on manufacturer's algorithm. The QFT indeterminates were incorporated in the analysis as either "not positive" or "not negative" depending if sensitivity or specificity of QFT was calculated, respectively. Suspected tuberculosis subjects are not considered in the calculation for specificity. Specificity was not evaluated in the TESEC-07 clinical trial as the trial was conducted in patients recently diagnosed with active tuberculosis.

Supportive analysis

A *post hoc* analysis of data pooled from the 3 pivotal clinical trials (TESEC-05, TESEC-06 and TESEC-07) was performed to assess SIILTIBCY's diagnostic performance. The QFT indeterminates were incorporated in the analysis as either "not positive" or "not negative" depending if sensitivity or specificity of QFT was calculated, respectively. Suspected tuberculosis subjects were not considered in the calculation for sensitivity or specificity.

Sensitivity
Sensitivity was evaluated in subjects with culture-confirmed active tuberculosis disease of TESEC-05 and TESEC-07 studies. The sensitivity of SIILTIBCY (n = 380) was 76.8% (95% CI: 72.6; 81.1) compared to 68.0% (95% CI: 64.0; 72.0) for QFT (n = 516) and 85.2% (95% CI: 81.6; 88.8) for PPD (n = 378). The percentage difference in sensitivity was 8.8% (95% CI: 2.7; 14.9) in comparison to QFT and -8.3% (95% CI: -14.2; -2.5) compared to PPD.

Special populations

Paediatric population
A total of 723 paediatric subjects (32 days to 2 years: 115 subjects; 2 to 4 years: 156 subjects; 5 to 11 years: 312 subjects; 12 to17 years: 140 subjects) were included in 2 Phase 3 trials, TESEC-05 and TESEC-06, with the aim to evaluate the diagnostic performance and the safety of SIILTIBCY in the paediatric population. The paediatric group received the same dose of SIILTIBCY as the adult group.

The induration was measured 2 to 3 days after SIILTIBCY administration and cut-off for a positive test was ≥ 5 mm.

The sensitivity and specificity of SIILTIBCY in different age groups were evaluated in a *post hoc* pooled analysis of the 3 pivotal clinical trials (TESEC-05, TESEC-06 and TESEC-07).

In children of 0 to 10 years of age, sensitivity of SIILTIBCY (n = 5) was 80.0% (95% CI: 44.9; 100.0) compared to 66.7% (95% CI: 13.3; 100.0) for QFT (n = 3) and 60.0% (95% CI: 17.1; 100.0) for PPD (n = 5). In individuals of 11 to 25 years of age, sensitivity of SIILTIBCY (n = 108) was 81.5% (95% CI: 74.2; 88.8) compared to 76.3% (95% CI: 69.1; 83.5) for QFT (n = 135) and 90% (95% CI: 84.1; 95.9) for PPD (n = 100).

In children of 0 to 10 years, specificity of SIILTIBCY (n = 85) was 81.2% (95% CI: 72.9; 89.5) compared to 72.3% (95% CI: 62.7; 81.9) for QFT (n = 83) and 84.7% (95% CI: 77.1; 92.4) for PPD (n = 85). In individuals of 11 to 25 years of age, specificity of SIILTIBCY (n = 241) was 98.3% (95% CI: 96.7; 100.0) compared to 95.9% (95% CI: 93.3; 98.4) for QFT (n = 241) and 97.4% (95% CI: 95.1; 99.6) for PPD (n = 191).

5.2 Pharmacokinetic properties

No pharmacokinetic study has been performed. Since SIILTIBCY is administered intradermally, the exposure is mostly local and very little systemic effect is expected.

5.3 Preclinical safety data

Non-clinical data on rdESAT-6 (administered subcutaneously to rat and dog) and the combination rdESAT-6 + rCFP-10 (administered subcutaneously to rat) reveal no special hazard for humans based on conventional studies of acute and repeated dose toxicity.
An embryo-foetal development study on the combination rdESAT-6 + rCFP-10 and vehicle phenol 0.5% (included in the commercial formulation) administered subcutaneously to rat, reveal no maternal toxicity nor embryo-foetal abnormalities. The estimated human equivalent dose at which no effects were observed in rats was 4.64 mcg/kg rdESAT-6 + rCFP-10 (more than 2 700-fold higher than the human dose) in the repeated dose toxicity studies, and 6.08 mcg/kg for rdESAT-6 + CFP-10 in the embryo-foetal development study (more than 3 500-fold higher than the human dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate dihydrate (E339)
Potassium dihydrogen orthophosphate (E340)
Potassium chloride (E508)
Sodium chloride
Polysorbate 20 (E432)
Phenol
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years.

After first opening

Chemical and physical in-use stability has been demonstrated for 28 days at 2 °C to 8 °C.

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2 °C to 8 °C. Other in-use storage times and conditions are responsibility of the user.

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 first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 mL solution in a clear multidose glass vial with stopper (bromobutyl rubber) and a plastic flip-off cap with aluminium over-seal. Each vial contains 10 doses of 0.1 mL.

Pack sizes

- 1 multidose vial
- Multipack containing 10 (10 packs of 1) multidose vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Upon discharge, patients should be instructed to keep the injection site clean. The scratching of the injection site should be avoided but in case of itching a cold compress can be applied.

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

The solution is to be discarded if visible particulate matter is observed.

7. MARKETING AUTHORISATION HOLDER

Serum Life Science Europe GmbH
Ahrensburger Strasse 1
30659 Hannover
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/24/1882/001
EU/1/24/1882/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 January 2025

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

Name and address of the manufacturer of the biological active substances

Serum Institute of India Pvt. Ltd.
212/2 Off Soli Poonawalla Road
Hadapsar
Pune-411028
India

Name and address of the manufacturer responsible for batch release

Bilthoven Biologicals B.V.
Antonie Van Leeuwenhoeklaan 9
3721 MA Bilthoven
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

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

SIILTIBCY (0.5 microgram + 0.5 microgram)/mL solution for injection
Mycobacterium tuberculosis derived antigens (rdESAT-6 and rCFP-10)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.1 mL) contains:

rdESAT-6: 0.05 microgram
rCFP-10: 0.05 microgram

Each vial (1 mL) contains 10 doses of 0.1 mL.

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate dihydrate, potassium dihydrogen orthophosphate, potassium chloride, sodium chloride, polysorbate 20, phenol, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 multidose vial (10 doses of 0.1 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intradermal use.
Read the package leaflet before 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

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.
After first opening, store in a refrigerator, use within 28 days.

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

Serum Life Science Europe GmbH
Ahrensburger Strasse 1
30659 Hannover
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1882/001 1 multidose vial (10 doses)

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 LABEL

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

SIILTIBCY (0.5 mcg + 0.5 mcg)/mL injection
rdESAT-6 / rCFP-10
Intradermal use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml multidose vial (10 doses of 0.1 mL)

6. OTHER

Once opened, store in a refrigerator, use within 28 days.
Discard date:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (MULTIPACK - WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

SIILTIBCY (0.5 microgram + 0.5 microgram)/mL solution for injection
Mycobacterium tuberculosis derived antigens (rdESAT-6 and rCFP-10)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.1 mL) contains:

rdESAT-6: 0.05 microgram
rCFP-10: 0.05 microgram

Each vial (1 mL) contains 10 doses of 0.1 mL.

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate dihydrate, potassium dihydrogen orthophosphate, potassium chloride, sodium chloride, polysorbate 20, phenol, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 10 (10 packs of 1) multidose vials.
Each vial contains 10 doses of 0.1 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intradermal use.
Read the package leaflet before 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

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.
After first opening, store in a refrigerator, use within 28 days.

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

Serum Life Science Europe GmbH
Ahrensburger Strasse 1
30659 Hannover
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1882/002 10 (10 x 1) multidose vials (multipack) (100 doses)

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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON (MULTIPACK - WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

SIILTIBCY (0.5 microgram + 0.5 microgram)/mL solution for injection
Mycobacterium tuberculosis derived antigens (rdESAT-6 and rCFP-10)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.1 mL) contains:

rdESAT-6: 0.05 microgram
rCFP-10: 0.05 microgram

Each vial (1 mL) contains 10 doses of 0.1 mL.

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate dihydrate, potassium dihydrogen orthophosphate, potassium chloride, sodium chloride, polysorbate 20, phenol, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 multidose vial (10 doses of 0.1 mL).

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intradermal use.
Read the package leaflet before 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

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.
After first opening, store in a refrigerator, use within 28 days.

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

Serum Life Science Europe GmbH
Ahrensburger Strasse 1
30659 Hannover
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1882/002 10 (10 x 1) multidose vials (multipack) (100 doses)

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

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

SIILTIBCY (0.5 microgram + 0.5 microgram)/mL solution for injection
Mycobacterium tuberculosis derived antigens (rdESAT-6 and rCFP-10)

▼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 skin test 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SIILTIBCY is and what it is used for
2. What you need to know before you receive SIILTIBCY
3. How SIILTIBCY is administered
4. Possible side effects
5. How to store SIILTIBCY
6. Contents of the pack and other information

1. What SIILTIBCY is and what it is used for

SIILTIBCY is for diagnostic use and contains as active substances two tubercular specific proteins (antigens) named rdESAT-6 and rCFP-10.

SIILTIBCY is injected in the skin (intradermally) to detect the infection (including disease) caused by *Mycobacterium tuberculosis* in adults and children aged 28 days and older.
For interpretation of test results it is used together with other medical procedures.
If a person has been infected with *Mycobacterium tuberculosis*, her/his immune system will respond by producing cytokines (inflammatory proteins) which cause induration (hardening) at the site where SIILTIBCY was injected that usually occurs 48 to72 hours after injection.

2. What you need to know before you receive SIILTIBCY

You should not receive SIILTIBCY
- if you are allergic to the active substances in SIILTIBCY, rdESAT-6, rCFP-10, or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to *Lactococcus lactis*, a bacteria used to make SIILTIBCY.
- if you have experienced a severe local (skin) or general (affecting anywhere in the body) reaction to other tuberculosis skin tests.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before being tested with SIILTIBCY if:
- you have had a SIILTIBCY testing within the last 6 weeks.
- you have been vaccinated within the last 4 weeks with live vaccines (such as vaccines against measles, mumps and rubella).
- you are taking any medicines (such as corticosteroids) or have any conditions that may suppress the immune system such as the human immunodeficiency virus (HIV).

Although not known to occur with SIILTIBCY, serious allergic reactions (anaphylaxis) such as swelling of the lips, face and throat, breathing difficulty, and hives have occurred in very rare cases with other tuberculosis skin tests. Tell the doctor or nurse who gave you this skin test immediately or contact the closest doctor or emergency department if you face one or more of these symptoms after being tested with SIILTIBCY.

Children and adolescents
There are no additional warnings or precautions applicable to children or adolescents.

Other types of mycobacteria (nontuberculous mycobacteria) and SIILTIBCY
SIILTIBCY is not suitable to be used to identify previous contact to types of mycobacteria that do not cause tuberculosis or prior vaccination with Bacillus Calmette-Guérin.

Pregnancy, breast-feeding and fertility
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 being skin tested.

It is not expected that performing the SIILTIBCY test during pregnancy and lactation has a damaging effect.

Driving and using machines
SIILTIBCY has no or negligible influence on your ability to drive and use machines.

SIILTIBCY contains potassium, sodium and polysorbate 20
This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
This medicine contains 0.011 mg of polysorbate 20 in each dose, which is equivalent to 0.11 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How SIILTIBCY is administered

The doctor or nurse will inject SIILTIBCY in the upper layer of the skin of your forearm.

The recommended dose is 0.1 mL. The dose is the same in all age groups.

After injection, a papule (raised bump on the skin) of 8-10 millimetres in diameter will appear and remain for about 10 minutes. Redness and induration (hardening of the skin) may appear at the injection site. After injection, your doctor or nurse may watch over you for at least 15 minutes to monitor for signs of an allergic reaction.

You should keep the injection site clean; do not scratch the injection site, and in case of itching a cold compress can be applied.

For test reading you should return after 48 to 72 hours to your doctor or nurse to check the result. If redness or an induration has appeared, it should decrease after this time.

Detailed information on the method of administration of SIILTIBCY and of evaluation of the result is included in the section "The following information is intended for medical or healthcare professionals only".

SIILTIBCY testing is not influenced by previous vaccination with Bacillus Calmette-Guérin (BCG) vaccine.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Although not known to occur with SIILTIBCY, serious allergic reactions (anaphylaxis) such as swelling of the lips, face and throat, breathing difficulty, and hives have occurred in very rare cases with other tuberculosis skin tests. If you experience any of these reactions, tell the doctor or nurse who gave you this skin test immediately or contact the closest doctor or emergency department.

Other side effects

Very common (may affect more than 1 in 10 people)
- Pruritus (itching) at the injection site

Common (may affect up to 1 in 10 people)
- Haematoma (bruising) at the injection site
- Vesicles (spots) at the injection site
- Headache
- Induration (skin hardness) at the injection site
- Swelling at the injection site
- Pain at the injection site
- Rash at the injection site
- Erythema (redness) at the injection site

Uncommon (may affect up to 1 in 100 people)
- Lymphadenopathy (swelling of the lymph nodes)
- Fever
- Ulcers at the injection site
- Haemorrhage (bleeding) at the injection site
- Malaise (general feeling of discomfort, illness or lack of well-being)
- Dizziness
- Rash
- Pruritus (itching)
- Myalgia (muscle pain)
- Fatigue (tiredness)
- Discolouration (discoloured skin) at the injection site
- Pain in the extremities (hands, arms, feet or legs)
- Pain
- Gastroenteritis (inflammation of the stomach and intestines)
- Diarrhoea
- Influenza-like (flu-like) illness
- Nausea (feeling sick)

Rare (may affect up to 1 in 1 000 people)
- Lymphadenitis (infection in lymph nodes)
- Hepatitis (inflammation of liver)
- Urticaria (itchy and raised red areas of skin) in any part of the body
- Pain in armpit
- Head discomfort
- Chills
- Hypoaesthesia (numbness at the injection site)
- Papule (raised bump) at the injection site
- Urticaria (itchy and raised red areas of skin) at the injection site
- Nodule (swollen lump) at the injection site

- Inflammation at the injection site
- Eosinophilia (increase in white blood cells)
- Night sweats
- Arthritis (pain and swelling in the joints)
- Vomiting
- Increased transaminases (increased blood levels of liver enzymes)
- Paraesthesia (numbness, tingling or prickling) in any part of the body
- Jaundice (yellow colour of skin and eyes)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 SIILTIBCY

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 carton and vial label 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.

Once opened, the vial can be used for up to 28 days provided it is stored in a refrigerator (2 °C – 8 °C).

Do not throw away any medicines via wastewater. 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 SIILTIBCY contains
- The active substances are *Mycobacterium tuberculosis* derived antigens rdESAT-6 and rCFP-10.
  One dose (0.1 mL) of SIILTIBCY contains 0.05 microgram rdESAT-6 and 0.05 microgram rCFP-10.
- The other ingredients are disodium hydrogen phosphate dihydrate (E339), potassium dihydrogen orthophosphate (E340), potassium chloride (E508), sodium chloride, polysorbate 20 (E432), phenol and water for injections. See section 2 “SIILTIBCY contains potassium, sodium and polysorbate 20”.

What SIILTIBCY looks like and contents of the pack
SIILTIBCY solution for injection (injection) is a clear, colourless to pale-yellow solution. This medicine should not be used if visible particulate matter is noticed.

SIILTIBCY is available in a pack of 1 multidose glass vial, or in multipacks containing 10 (10 packs of 1) multidose glass vials, each containing 1 mL.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Serum Life Science Europe GmbH
Ahrensburger Strasse 1
30659 Hannover

Germany

Manufacturer
Bilthoven Biologicals B.V.
Antonie Van Leeuwenhoeklaan 9
3721 MA Bilthoven
The Netherlands

This leaflet was last revised in

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

The following information is intended for healthcare professionals only

SIILTIBCY should be prepared and administered via intradermal injection by healthcare professionals trained for the Mantoux technique. The medicinal product should be administered with adequate hygiene of the hands and using aseptic technique, as follows:

- Withdraw 0.1 mL of SIILTIBCY using a 1 mL syringe with a short-bevel needle. Before drawing SIILTIBCY from the multidose vial, expel any air from the syringe. If the vial was already opened, swab it with an alcohol swab and let it dry before use.
- Administer the 0.1 mL of SIILTIBCY intradermally in the middle-third of the forearm using the Mantoux technique. Therefore, stretch the skin slightly and hold the needle almost parallel to the skin surface with the bevel upwards. Insert the tip of the needle into the superficial layer of the dermis. Make sure the needle is visible through the epidermis during the injection. Do not apply the test in areas of scars, rashes, burn or tattoos.
- Inject the drawn 0.1 mL solution slowly. A small-blanched papule of 8-10 millimetres in diameter will appear, which should disappear after about 10 minutes. If the papule does not appear, repeat a new injection of 0.1 mL SIILTIBCY on the other arm or on the same arm at least 4 cm away from the first injection site.

Close observation of the subject for at least 15 minutes is recommended following the test.

Evaluating the reaction
Intradermally injected SIILTIBCY may induce an induration at the site of injection. The induration can be seen as a raised area with clearly defined margin at and around the injection site. Although erythema can accompany the induration, only the induration should be measured.

The induration should be measured 48 to 72 hours after the injection. Measure the diameter of the induration transversely to the long axis of the forearm with a ruler. To allow ease with measurement, a flexible (or easily bendable) ruler is suggested.

Normally the induration and erythema will decrease after 4 days and disappear within 28 days after the injection.

Interpretation
An induration of ≥ 5 mm is considered as a positive test result, which indicates infection with *Mycobacterium tuberculosis*.