For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

rdESAT-6 and rCFP-10 (Cy-Tb) Injection

Cy-Tb™

1. NAME OF THE MEDICINAL PRODUCT
rdESAT-6 and rCFP-10 (Cy-Tb) Injection,
solution for intradermal injection for Mantoux Test

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One single test dose (0.1 mL) contains:
rdESAT-6: 0.05 µg
rCFP-10: 0.05 µg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Clear, colourless to yellow solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Detection of Latent-tuberculosis for population of 18 years and above.

4.2 Posology and method of administration
The test dose is 0.1 mL.
The medicinal product is for diagnostic use only

Method of administration for Test
Cy-Tb is administered via intradermal injection using the Mantoux technique as follows:

- Administer 0.1 mL of Cy-Tb using a 1 mL syringe with a short-bevel 26 or 27 gauge size needle.
- Inject Cy-Tb in the middle-third of the forearm.
- 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.
- Inject the drawn 0.1 mL solution slowly. A small-blanched papule of 8 - 10 millimeters in diameter will appear, which should disappear after about 10 minutes. If the papule does not appear, repeat the injection on the other arm or on the same arm at least 4 cm away from the first injection site.

Evaluating the reaction
Intradermal injected Cy-Tb 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 - 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*.
A repeat Cy-Tb test can be performed in population with a negative result at interval of at least 6 weeks. This population includes individuals in a screening program such as health care professionals and contacts to active TB cases (i.e. index case).

Special populations
In HIV$^+$ individuals with a CD4$^+$ T-cell count below 100 T-cells/mm^3 may have an increased risk of false-negative results. A positive test result indicates infection with *Mycobacterium tuberculosis* regardless of the CD4$^+$ T-cell count.

4.3 Contraindications
Potential recipient of Cy-Tb with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1 should not be administered Cy-Tb.
Cy-Tb is produced in *Lactococcus lactis* therefore, people with known allergy to *Lactococcus lactis* should not be administered Cy-Tb.

4.4 Special warnings and precautions for use
Anaphylactic, anaphylactoid or other allergic type reactions are theoretically possible following administration of Cy-Tb. Close observation for at least 15 minutes is recommended following the test. As with all injectable medicinal products, appropriate medical treatment and supervision should always be readily available.
Adherence to the Mantoux technique when administering Cy-Tb is essential for obtaining reliable results, therefore avoid subcutaneous or intramuscular injection.

4.5 Interaction with other medicinal products and other forms of interaction
There are no known interactions with other medicinal products with Cy-Tb.
However, a risk of false-negative test results may occur if Cy-Tb is administered in patients undergoing treatment that affects their immune system.

4.6 Pregnancy and lactation
Fertility
Animal studies have not revealed any evidence of impaired female fertility.
Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of Cy-Tb in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Lactation
No effects on the breastfed newborns/infants are anticipated since the systemic exposure of the breastfeeding woman to Cy-Tb is negligible.

4.7 Effects on ability to drive and use machines
Cy-Tb 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 is based on data from subjects (aged 28 days to 65 years) who participated in clinical trials. Adverse reactions experienced after receiving Cy-Tb are generally mild and transient.
Adverse drug reactions are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000) and not known (cannot be estimated from available data).

Tabulated list of adverse reactions

MedDRA SOC	Frequency	Adverse reactions
General disorders and administration site conditions	Very Common	Injection site pruritus
	Common	Injection site pain, injection site hematoma, injection site rash, injection site vesicles, injection site erythema, injection site swelling
	Uncommon	Injection site induration, pyrexia, injection site haemorrhage, malaise, injection site ulcer, injection site discolouration, influenza like illness, pain, fatigue
	Rare	Injection site inflammation, injection site anaesthesia, axillary pain, injection site papule, injection site nodule, injection site urticaria, chills
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Rare	Paraesthesia, head discomfort
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, rash
	Rare	Urticaria, night sweats
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy
	Rare	Eosinophilia, lymphadenitis
Infections and infestations	Uncommon	Gastroenteritis
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia, pain in extremity
	Rare	Arthritis
Gastrointestinal disorders	Uncommon	Diarrhoea
	Rare	Nausea, vomiting
Investigations	Uncommon	Transaminases increased
	Rare	Eosinophil count increased
Hepatobiliary disorders	Rare	Hepatitis, jaundice

Description of selected adverse reactions
Induration and erythema are expected reactions in individuals infected with *M. Tuberculosis*. Induration more than 50 mm and erythema more than 80 mm may occur in uncommon cases, which normally would decrease after 4 days and disappear within 28 days.

Other special population
Frequency, type and severity of adverse reactions in HIV$^+$ population are expected to be the similar to those in adult population.

4.9 Overdose
Overdose due to Cy-Tb injection is not expected mainly because of the nature of the intradermal injection.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Tuberculosis diagnostics, ATC code not yet assigned.

Technical performance
Cy-Tb is administered via intradermal injection using the Mantoux technique (please see 4.2 for more information).

Mechanism of action
In case of infection with *Mycobacterium tuberculosis*, Cy-Tb induces a delayed-type hypersensitivity reaction directed by cytokines, which are released by TH1 cells after stimulation by specific antigens. This reaction is seen as an induration at the site of injection. The induration reaches its maximum 48 - 72 hours after administration.

Clinical efficacy
A positive Cy-Tb test indicates infection with *Mycobacterium tuberculosis*.
The test result is not influenced by previous BCG vaccination.
A positive Cy-Tb test is defined as any induration diameter of 5 mm or above.
A negative Cy-Tb test is defined as any induration diameter below 5 mm.

Clinical trials
Cy-Tb ability to identify individuals infected with *Mycobacterium tuberculosis* has been investigated in seven clinical trials involved individuals from 28 days up to 65 years of age. In total, 2960 individuals have received Cy-Tb. The population included were negative controls, positive controls, or as occasionally or close contacts. In all trials, indurations have been measured 48 - 72 hours after administration of Cy-Tb. Subgroups included in the clinical trials were paediatric population (28 days - 17 years) and HIV$^+$ individuals.
In two trials, specificity (patients with confirmed *Mycobacterium tuberculosis* infection) and sensitivity (negative control population) were investigated. The aim of these two trials was to identify the optimal induration cut-off. The specificity was estimated to 99.3% (CI: 96.3 - 100.0) and the sensitivity was estimated to 73.9% (CI: 67.8 - 79.3). The optimal cut-off for injection site induration was ≥ 5 mm.
In one trial, the relationship between Cy-Tb test positives and the risk of *Mycobacterium tuberculosis* infection was investigated. Four groups were included based on the exposure rate to *Mycobacterium tuberculosis* (negative population, confirmed Mycobacterium tuberculosis infected population, and occasionally or close contacts). Cy-Tb showed a strong correlation with the exposure to *Mycobacterium tuberculosis*.

Paediatric population
A total of 723 children in the age group of 28 days - 17 years were included in two phase III trials, with the aim to evaluate the diagnostic performance and the safety of Cy-Tb in the paediatric population. The paediatric group received the same dose of Cy-Tb as the adult group. The induration was measured 48 - 72 hours after Cy-Tb administration and cut-off for a positive test was ≥ 5 mm. The paediatric population followed the same schedule as the adult population. The trials concluded that the from the age of 8 months, sensitivity can be fully extrapolated from the adult population, and from 28 days specificity can be fully extrapolated from adult population. Below 8 months, the sensitivity will decrease which could increase false-negative test results. However, a positive test should be an indication of infection with Mycobacterium tuberculosis independent of age. No specific safety issues were seen in the paediatric population compared to the adult population.

Special population
A total of 459 HIV$^+$ individuals were included in three trials. In all HIV$^+$ individuals T-cell count was performed. The aim was to evaluate the ability to respond towards Cy-Tb according to T-cell count. Induration sizes among Cy-Tb responders seemed unaffected by HIV status even though HIV infection increased the number of non-responders. The size of Cy-Tb indurations appeared constant among HIV$^+$ responders with CD4$^+$ T-cell counts above 100 cells/mm^3. No specific safety issues were seen in the HIV$^+$ population compared to the adult population.

5.2 Pharmacokinetic properties
Not applicable

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity and embryo-foetal toxicity.
In non-clinical studies, no effect on female fertility or offspring was observed after Cy-Tb administration.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Disodium hydrogen phosphate dihydrate
Potassium dihydrogen orthophosphate
Potassium chloride
Sodium chloride
Polysorbate 20
Phenol
Water for injection

6.2 Incompatibilities
This medicinal product must not to be mixed with other products in the same syringe.

6.3 Shelf-life
Unopened vial: 15 months
After first opening, the vial can be used for up to 28 days provided it is stored between 2°C - 8°C.

6.4 Special precautions for storage
Store in a refrigerator (+2° to +8°C).
Do not freeze.
Store in original package in order to protect from light. For storage condition after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container
1 mL multidose vial (10 tests).

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION NUMBER(S)
Permission No.: MF/ND/58/2022

8. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
Date: 09 May 2022

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