For the use only of a registered medical practitioner or a Hospital or a Laboratory

Mycobacterium w (Heat Killed) Injection

Sepsivac™
(Heat killed Mw)

1. Description:

Mycobacterium w (Heat Killed) Injection is a colourless opaque suspension in which *Mycobacterium w* cells are suspended and having tendency to settle down during storage.

2. Qualitative and Quantitative composition:

Each 0.1 mL contains:

Mycobacterium w (Heat Killed)	:	0.5×10^9 bacilli
Sodium Chloride IP	:	0.9 % w/v
Thiomersal IP (As Preservative)	:	0.01 % w/v
Water for injections IP	:	q.s

3. Dosage form and strength:

Mycobacterium w (Heat Killed) injection is a sterile suspension for intradermal injection. The strength of *Mycobacterium* w (Heat Killed) injection is 0.5×10^9 Cells per 0.1 mL.

4. Clinical particulars:

4.1 Therapeutic Indication:

Mycobacterium w (Heat Killed) injection is used as immunotherapeutic agent in the following disease conditions:

1. Leprosy – in Lepromin negative patients
2. Advanced Non-Small Cell Lung Cancer (NSCLC) - in combination with Paclitaxel plus Cisplatin regimen
3. Sepsis (due to gram Negative infections) - as adjuvant to the standard treatment

4.2 Posology and method of administration :

Posology:

1. **Leprosy**
   The first dose of *Mycobacterium w* (Heat Killed) injection is administered by two intradermal injections. i.e. each 0.1mL administered at left and right hand of deltoid regions. Further, 0.1mL of *Mw* (Heat Killed) injection is administered in one deltoid area every 3 months interval for 2 years or advised by physician. After initial dose, total of 8 doses is recommended to be taken at 3 monthly interval along with regular multi drug therapy multi drug therapy (MDT).

2. **Non-Small cell lung cancer (NSCLC)**
   Adult and Geriatric patients (18 years and above)

   It is administered intradermally. It is advisable to inject 0.1 mL of the drug per site. The amount of the drug to be administered at one time and its frequency of administration are described to be dependent on therapeutic condition.

   Usually 0.2 mL of *Mycobacterium w* (Heat Killed) injection is recommended to be given initially in two-divided dose of 0.1 mL on each arm followed by 0.1 mL subsequently. The initial dose of 0.2 mL will be given prior to one week of onset of chemotherapy and subsequent dose of 0.1 mL each will be administered in adjuvant to four cycles of chemotherapy (Cisplatin and Paclitaxel) including 3 week (21 days) each cycle. *Mw* (Heat Killed) injection is recommended to be taken at 2nd and 3rd week of each cycle (Intradermal 0.1 mL in deltoid).

   Mw (Heat Killed) injection should be administered monthly after completion of all chemotherapy cycles (four cycle) till 12 months from start of treatment.

3. **Severe Sepsis:**
   A 0.3 ml of Mycobacterium w (Heat Killed) injection is given intradermally in three divided doses of 0.1 ml each on three different sites daily for three days. Total dose is 0.9 ml of Mycobacterium w over a period of three days. Mw (Heat Killed) injection is recommended to be prescribed in patient with age 18-65 years.

Method of administration

The recommended site for giving the *Mw* (Heat Killed) injection is at the insertion of the deltoid muscle near the middle of the left upper arm. Sites higher on the arm are more likely to lead to keloid formation, the tip of the shoulder particularly. For cosmetic reasons, a scar on the upper and lateral surface of the thigh may be preferred and this is an alternative site.

The upper arm must be approximately 45 degrees to the body. This can be achieved if the hand is placed on the hip with the arm abducted from the body. The skin should be swabbed with spirit and allowed to dry. It is advisable to use 26 G or smaller gauge (27 G, 30 G) needle. The operator stretches the skin between the thumb and forefinger of one hand and with the other slowly inserts the needle, with the bevel upwards, till bevel is fully in the demises and not visible out. The needle can usually be seen through the epidermis. A correctly given intradermal injection results in a tense blanched raised bleb (Peau D'Orange) and considerable resistance is felt when the fluid is being injected.

A bleb typically of 7 mm diameter follows a 0.1 mL injection. If little resistance is felt when injecting and a diffuse swelling occurs as opposed to a tense blanched bleb, the needle is too deep. The needle should be withdrawn and reinserted intradermally before more is injected. The subject must always be advised of the normal reaction to the injection. The second dose of injection is to be given one inch apart from previous dose to minimize the chance of local reaction.

This injection must be given strictly intradermally.
Injection site reaction and care of the injection site:
Following intradermal administration of *Mw* (Heat Killed) injection, normally a local reaction develops at the immunization site within two to six weeks, beginning as a small papule which increase in size for a few weeks widening into a circular area with scaling, crusting and occasional bruising. Occasionally a shallow ulcer develops. It is not necessary to protect the site from becoming wet during washing and bathing, but should any oozing occur, a temporary dry dressing may be used until a scab forms. It is essential that air be not excluded. If absolutely essential an impervious dressing may be applied but only for a short period (for example, to permit swimming) as it may delay healing and cause a larger scar. The lesion slowly subsides over several months and eventually heals leaving only a small, flat scar.

4.3 Contraindications:

Mycobacterium w (Heat Killed) injection is contraindicated in

- History of allergic reactions attributed to *Mycobacterium w* (Heat Killed) injection or any of the excipients in the formulation mentioned in section 2
- Individuals with fever
- Pregnant and Lactating women
- Individuals with generalized septic skin conditions (if eczema exists, a site should be chosen that is free from skin lesions).
- Patient with chronic debilitating condition other than the proposed indication

4.4 Special warnings and precautions for use:

Injection site reaction and care of the injection site:

Please see section 4.2 (posology and method of administration) for details information

Severe injection site reactions, large ulcers and abscess are most commonly caused by faulty injection technique. Hence adequate precaution should be taken while intradermal injections and should be administered by a healthcare staff well trained in the procedure.

Mycobacterium w (Heat Killed) injection can cause erythema, induration and ulceration of the skin at site of injection which are usually mild and can be self-healing. If the condition is not cured then please consider supporting therapy and necessary antibiotics.

Mycobacterium w (Heat Killed) injection is not recommended to be administer via Intravenous, subcutaneous, intramuscular injection.

The intradermal injection can also cause minor active local reactions and local delayed type hypersensitivity reaction, type I and II reaction, neuritis. If condition get worsened or not self-cured please provide patient with proper supporting drug therapy.

4.5 Drug interactions:

Mycobacterium w (Heat Killed) injection is not known to have any drug-drug interactions. It is able to induce body's own immune response even when administered with other drugs like cytotoxic, anti-leprosy drugs.

4.6 Use in special populations:

Animal reproduction studies have not been conducted with *Mycobacterium w* (Heat Killed) injection. It is also not known whether *Mycobacterium w* (Heat Killed) injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

It is not known whether drug is excreted in human milk. As many drugs are excreted in human milk, caution should be exercised when drug is administered to a nursing woman.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed with *Mycobacterium w* (Heat Killed) injection.

4.8 Undesirable effects:

It has been found to be generally well tolerated and free from severe systemic adverse effects in Leprosy treatment. The only side effects encountered were injection site erythema and ulceration. The erythema appeared after 48 hours of injection and was followed by induration by 7th day culminating into the formation of a shallow, self-healing ulcer in the 3rd week which healed with scab formation in the 4th week leaving a scar, as observed in clinical trials.

Severe injection site reactions, large ulcers and abscesses are most commonly caused by faulty injection technique where part or the entire dose is administered too deeply.

Keloid formation at the injection site is an uncommon and largely avoidable, complication of *Mw* (Heat Killed) injection. Some sites are more prone to keloid formation than others and those using *Mw* (Heat Killed) injection should adhere to the two sites recommended. (The mid-upper arm or the thigh). Most experience has been gained in the use of the upper arm and it is known that the risk of keloid formation is increased manifold when the injection is given at a site higher than the insertion of the deltoid muscle near the middle of the upper arm.

Clinical trials conducted in patients with NSCLC has shown anaemia, Leukopenia, Neutropenia, as treatment-emergent haematological toxicities (*Mycobacterium w* (Heat Killed) injection with paclitaxel and cisplatin or paclitaxel and cisplatin). Out of which, anaemia was the most commonly reported. There were no grade 3 neutropenia cases reported in test arm whereas 2 cases of neutropenia (*Mycobacterium w* (Heat Killed) injection with paclitaxel and cisplatin) were reported in control arm (paclitaxel and cisplatin). The overall incidences of grade 3 and 4 non-haematological laboratory toxicities were low in both arms. Among the two arms, the most common grade 3 and 4 non-haematological toxicities were increased transaminase and alkaline phosphatase levels. Clinical Adverse Events includes nausea and vomiting, diarrhoea, pain, weakness, weight loss, anorexia, neuropathy, Constipation, Breathlessness, Loss of appetite, Cough, Haemoptysis, Reactogenic reactions, Neuropathy and alopecia were observed in test arm. Out of these, Reactogenic reactions (96 out of total 277 adverse events), Nausea and Vomiting (56 out of total 277 adverse events) were most common. All these adverse events were grade 1 and 2. Only 2 patients experienced grade 3 (Diarrhoea and cough) adverse events.

In randomized, double-blind, comparative study conducted in patient with sepsis, the Mw group had significantly lesser incidence of secondary bacterial infection compared with the control group. Ventilator associated pneumonia (VAP) was the commonest secondary bacterial infection in both groups; 12 patients in the control group developed VAP, whereas 5 patients in the Mw group had occurrence of VAP. Acinetobacter baumannii was the commonest organism responsible for nosocomial infections. Catheter-related blood stream infection (CRBSI) occurred in 2 and 6 cases in the Mw and control groups, respectively. Six patients had both VAP and CRBSI: 2 in the Mw group and 4 in the control arm. In another Clinical Trial (Phase IIa) conducted in patient with sepsis a total of 30 out of 72 randomized patients reported adverse events which includes transfusion associated reaction, Thrombocytopenia, Hypokalemia, Transaminitis, Local site reaction, Hyponatremia, Hypokalemia, Respiratory system involvement, Derranged RFT. All the reported adverse events were mild and none were severe. Local injection site reactions were found to be probably related with the study drug. Transaminitis and Thrombocytopenia were possibly related with study drug (standard treatment and 0.1 ml of MW injection). In another clinical trial (phase IIb) conducted in patient with severe sepsis, twenty seven (27) SAEs were observed. Out of these, eight (08) SAEs were observed in Test treatment arm and nineteen (19) SAEs were observed in Control arm. This indicates Mycobacterium w (Heat Killed) injection is found to be safe and well tolerated, without any major safety concerns in patients with severe sepsis.

4.9 Overdose:

No data is available on overdose with *Mycobacterium w* (Heat Killed) injection.

5. Pharmacological properties

5.1 Mechanism of Action:

Immunomodulators or biological response modifiers have been in vogue since long. They work by altering biological response of individuals to various pathological conditions/disease. *Mycobacterium* w (Heat Killed) Injection is one of

such agent. It contains heat killed *Mycobacterium w* was an active drug substance. It elicits potent cell mediated immune response when administered intradermally. Cell mediated immune response are designated as the Th1 type or Th2 type depending on the cytokines liberated by excited T cells. Interferon Gamma & Interleukin - 2 are cytokines associated with Th1 response. In normal healthy individuals there is a harmony between Th1 response and Th2 response. Certain diseases are associated with decreased Th1 response. They include Malignancy and Leprosy. Improving Th1 response in such conditions is associated with improved outcomes.

5.2 Pharmacodynamics Properties:

Mycobacterium w (Heat Killed) shares antigens with *M. Tuberculosis* as well as *Mycobacterium Leprae*. In experimental models it is found to induce lympho-proliferative response. The lymphoproliferative response induced by *Mycobacterium w* (Heat Killed) is the most potent of all known immune modulators. It provides immunity against tuberculosis in animals. The protection provided against tuberculosis by *Mycobacterium w* (Heat Killed) is universal. It is seen in all species & strains. BCG also provides protection in animals. However, protection provided by BCG is species and strain specific and not universal. *Mycobacterium w* (Heat Killed) injection provides protection against tuberculosis in species and strains of animals in which BCG works as well as in species and strains in which BCG fails to provide protection.

Cell mediated immune response are designated as the Th1 type or Th2 type depending on the cytokines liberated by excited T cells. Interferon Gamma & Interleukin - 2 are cytokines associated with Th1 response. In normal healthy individuals there is a harmony between Th1 response and Th2 response. Administration of *Mycobacterium w* (Heat Killed) is also associated with release of Th1 type cytokines like Interferon Gamma and Interleukin - 2.

Clinical Studies in LEPROSY

Mycobacterium w (Heat Killed) injection exhibits an immune stimulant effect as shown by conversion of lepromin negative reaction into positive. In a clinical study of lepromin-negative BB (Borderline) leprosy patients, 75% patients became lepromin positive after the first dose, 81 % after the second dose and l00% after the third dose. In BL (Borderline Lepromatous) leprosy the conversion rates were 43%, 60% and 82% after the first, second, and third doses of *Mycobacterium w* (Heat Killed) injection, respectively.

Lepromin conversion in response to *Mycobacterium w* (Heat Killed) injection is attributed to the presence of the "right mix" of antigenic determinants in .the preparation which stimulate cell mediated immunity (CMI). This leads to histopathological upgrading and clearance of dermal granuloma without the risk of hypersensitivity reactions which could lead to nerve damage.

Clinical trials have revealed the beneficial effects of immunomodulation with heat killed *Mycobacterium w* (Heat Killed) in accelerating the bacillary clearance and shortening the duration of therapy in multibacillary leprosy. It has been shown to produce statistically significant ($p<0.001$) bacteriological fall in LL and BL leprosy from 6 months onwards.

Histopathologically, the addition of *Mycobacterium w* (Heat Killed) injection to MDT (multi-drug therapy), has shown a higher and statistically significant upgradation in LL and BL leprosy (P<0.00 l) and complete clearance of granuloma as compared to patients treated only with MDT. Therefore, *Mycobacterium w* (Heat Killed) injection is recommended as an adjunct to MDT in multibacillary leprosy to induce an early bacteriological clearance and shorten the duration of therapy.

Clinical Studies in NSCLC

Study 1 - Between January 2005 and June 2005, patients with advanced NSCLC were randomized to 2 arms. In arm A, 26 patients were randomized to receive Cisplatin 75 mg/m^2 on Day 1, and Etoposide 100 mg/m^2 on Days 1-3. The cycle was repeated every 21 days. *Mycobacterium w* (Heat Killed) Injection 0.1 mL was administered intradermally every 14th day for 6 months. In arm B, 22 patients were randomized to Cisplatin 75 mg/m^2 on Day 1 and Etoposide 100 mg/m^2 on Days 1-3. The cycle was repeated every 21 days.

Mycobacterium w (Heat Killed) injection improved response rate of chemotherapy by 11% (38% in *Mycobacterium w* (Heat Killed) injection arm vs 27% in control arm). *Mycobacterium w* (Heat Killed) injection also improved median survival by 4 months (11 months in *Mycobacterium w* (Heat Killed) injection arm vs 7 months in control arm).

The improvement in response rate and improved median survival seen in *Mycobacterium w* (Heat Killed) injection arm were associated with lower incidence of hematological and non- hematological toxicities as compared to the control arm.

Use of *Mycobacterium w* (Heat Killed) injection improves response rate and median survival in NSCLC.

Study 2 - Patients with advanced NSCLC were randomized to 2 groups. The treatment group (n=9) received chemotherapy (cisplatin-etoposide) and radiotherapy. *Mycobacterium w* (Heat Killed) injection was administered intradermally. The control group (n=10) received chemotherapy (cisplatin-etoposide) and radiotherapy. The *Mycobacterium w* (Heat Killed) group had better tolerance to therapy (Interruption of therapy in 50 % vs 0%). At the end of therapy 67 % responded to therapy in *Mycobacterium w* (Heat Killed) arm compared to none in control arm. The lung function improved in all the 9 patients in *Mycobacterium w* (Heat Killed) arm. The response seen in *Mycobacterium w* (Heat Killed) arm were durable in nature as seen to be stable during follow up at (6 months or more).

Study 3 - Two hundred and twenty-one treatment naïve patients with stage IIIB and IV NSCLC were randomized to receive paclitaxel and cisplatin with or without *Mycobacterium w* (Heat Killed) injection administered intradermally, 0.1 mL on each deltoid on the first visit at least 1 week prior to 1st cycle and then on day 8 and 15 of each cycle of chemotherapy. The cycles were repeated every 3 weeks for a total of 4 cycles. *Mycobacterium w* (Heat Killed) injection was administered once a month thereafter until progression or for a maximum of 12 months from the start of treatment in the investigational arm. The primary endpoint of the study was overall survival (OS) and the secondary outcome measures were response rate (RR) and progression free survival (PFS). One hundred twelve pts were randomized to the control arm and 109 pts to the *Mycobacterium w* (Heat Killed) arm.

Mycobacterium w (Heat Killed) injection improved response rate by 11% (36% in the control arm vs. 47% in the *Mycobacterium w* (Heat Killed) arm). There were three complete responses, all in the *Mycobacterium w* (Heat Killed) arm. Use of *Mycobacterium w* (Heat Killed) injection was associated with improvement in survival also. Improvement in Median PFS with use of *Mycobacterium w* (Heat Killed) was 96 days [p=0.0446; HR 0.43 (95% CI 0.25-0.73)] from 157 days in control arm to 253 days in *Mycobacterium w* (Heat Killed) arm. Use of *Mycobacterium w* (Heat Killed) also improved median survival by 59 days [p=0.0034; HR 0.55 (95% CI 0.37-0.82)] from 236 days in control arm to 295 days in the *Mycobacterium w* (Heat Killed) arm.

The improvement in response rate and survival seen with *Mycobacterium w* (Heat Killed) Injection were associated the adverse events comparable to the control arm.

Use of *Mycobacterium w* (Heat Killed) injection in patients with advanced NSCLC is safe and results in both improvement in progression free survival and overall median survival.

Clinical studies in SEVERE SEPSIS

Study 1 - Phase IIa study with 72 patients having gram negative severe sepsis/septic shock were enrolled in 3 groups (escalating dose levels 0.1, 0.2 and 0.3 *Mycobacterium w* (Heat Killed) injection over initial 3 days with standard therapy versus standard therapy alone). Significant early clinical and microbiological resolution was seen

in both 0.2 and 0.3 groups (p=0.0001). SOFA scoring clearly showed that patients receiving 0.3 *Mycobacterium w* (Heat Killed) injection had earliest decrease in scores with 83% of the patients recovering on day 15 and 100% on day 22 as compared to other groups receiving lesser doses as well as the standard treatment group. Patients receiving 0.3 *Mycobacterium w* (Heat Killed) injection dose had significant early recovery of organ function including renal and respiratory, multisystem organ failure, fever, and there was an early improvement of SOFA score. Patients receiving 0.2 *Mycobacterium w* (Heat Killed) injection dose also had statistically significant improvement in early recovery in hepatic, respiratory, cardiovascular, multisystem organ failure and fever. Patients receiving 0.1 mL dose had marginal early recovery as compared to the standard treatment group although it was not statistically significant except in case of fever. Mild local reactions were seen in 2 patients in 0.1 group, 3 patients in 0.2 group and 2 patients in 0.3 group. There was no serious adverse events observed. Cytokine levels were significantly elevated at baseline in all the groups which was more significant fall in 0.3 group compared to other treatment group. It was concluded that 0.3 *Mycobacterium w* (Heat Killed) injection dose seems to be efficacious in early organ function recovery and microbiological resolution among all the groups studied. Moreover, *Mycobacterium w* (Heat Killed) injection may serve as a promising novel immunomodulatory therapy in improving outcome in sever Gram Negative Septic Shock.

Study 2 - Patients were randomized 1:1 to the experimental (*Mycobacterium w* (Heat Killed) with standard therapy) or the control arm (standard therapy). Fifty patients with severe sepsis (25 *Mycobacterium w* (Heat Killed), 25 control) were included in the study. There were 7 and 8 deaths in the *Mycobacterium w* and control groups, respectively (p=0.51). The days on mechanical ventilator were significantly lesser in the *Mycobacterium w* (Heat Killed) group compared with control (median, 6 vs 9; p = 0.025). The median ICU and hospital length of stay was significantly less in the *Mycobacterium w* (Heat Killed) arm (7 vs 12 days [p=0.006] and 10 vs 16 [p=0.007], respectively). The delta SOFA score was significantly higher in the control arm (p=0.027). There was a higher incidence of secondary bacterial infections in the control group (P=0.009). Therefore, the use of *Mycobacterium w* (Heat Killed) in severe sepsis was associated with significant reduction in days on mechanical ventilation, ICU and hospital length of stay, lower incidence of nosocomial infection, and delta SOFA score.

Study 3 - Patients were randomized 1:1 to the experimental (*Mycobacterium w* (Heat Killed) with standard therapy) or the control arm (standard therapy). One hundred one patients with severe sepsis due to Gram Negative Bacteria (101 *Mycobacterium w* (Heat Killed), 101 control) were included in the study. There were 8 and 18 deaths in the *Mycobacterium w* (Heat Killed) and control groups, respectively. The primary end point of the study (28 days mortality) using *Mycobacterium w* (Heat Killed) as an adjuvant to standard treatment in sepsis to reduce the 28 days mortality associated with sepsis was met. The difference between the two treatment arms was 10.89% (absolute reduction) and 55.56% (relative reduction) which is clinically relevant and statistically significant. (*p = 0.0229*) There was significant difference in time to discharge (*p = 0.0001*) and time to discontinuation of vasopressor treatment (*p = 0.0159*) between the two arms, while no significant difference was found in ICU days and Ventilator days between the two arms. The observed difference is probably due to higher and early mortality in the control arm. The reduction in mean SOFA score from baseline to day 28 is observed in both arm. However, the reduction in SOFA score is significantly more in Treatment Arm as compared to Control Arm (*p=0.0182* at day 14, *p=0.0079* at day 21 and *p=0.0181* at day 28). Therefore, the use of *Mycobacterium w* (Heat Killed) in severe sepsis was associated with significant reduction in days on mechanical ventilation, ICU and hospital length of stay, lower incidence of SOFA score.

5.3 Pharmacokinetic properties
Not applicable

6. Non Clinical Properties

6.1 Animal Toxicology or Pharmacology:
Non-clinical data reveals no special hazard for human based on conventional studies like acute toxicity studies in mice & rats and subacute toxicity studies in mice & rabbits.

7. Pharmaceutical particulars

7.1 Incompatibilities.
Mycobacterium w (Heat Killed) Injection is not recommended to be diluted with any i.v. fluids.

7.2 Shelf life
The shelf life of *Mw* (Heat Killed) injection is 36 months when stored at +2^{0}C to +8^{0}C.

7.3 Packaging Information
0.6 mL of *Mycobacterium* w (Heat Killed) Injection is presented in USP type 1 glass vial.

7.4 Storage and handling instructions
Store at +2^{0}C to +8^{0}C.
Do not freeze.
Discard if frozen.
Shake well before use.
Keep out of reach of children.
Protect from light
Do not use *Mw* (Heat Killed) injection after the expiration date shown on the label.

8. Patient Counselling Information.
Consult the physician for personalized medical advice

9. Manufacturer:

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10. Market authorization with date
MF/BIO/19/000057 dated 28-Nov-2019

11. Last Revision details:
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