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LeImmune-T

Natural Killer Cells mediated

Innate Immunity Booster for

**improving/restoring activity of Natural Killer Cells/Innate Immunity against any virus –
including Novel Coronavirus**

We have released a Natural Killer Cells Activity/Innate Immunity Booster made from Tomato by name “LeImmune-T”.

Regulations applicable to LeImmune-T are:

(A) Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016 (“The Regulation A”, hereafter).

“LeImmune-T” is an extract of tomato in edible oil containing at least 418 µg bioavailable β-carotene dissolved in edible oil, is a Nutraceutical listed at No. 164 in Schedule VI of The Regulation A. It may further contain permitted additives.

(B) Food Safety and Standards (Advertising and Claims) Regulations, 2018 (“The Regulation B”, hereafter)

LeImmune-T, is labeled with a claim on “improves/restores activity of Natural Killer Cells/Innate Immunity capable of killing cells infected by any virus (Novel Coronavirus is a virus), bacteria and initial stage cancer cells” which reads as follows:

“There is Significant Scientific Agreement that beta carotene improves/restores activity of Natural Killer Cells activity in Innate Immunity compromised persons. Daily consumption of 200 g purple sweet potato leaves containing 23.42 mg β-Carotene improved the lytic activity of Natural Killer cells within 15 days in a human clinical trial (Chen et al.; World J Gastroenterol October 7, 2005 Volume 11 Number 37). From 56 molecules contained in green leafy vegetables, 1 molecule of beta carotene (that gives two molecules of Vitamin A) is bioavailable (GuangwenTang 2010; Am J Clin Nutr 2010;91(suppl):1468S–73S. Provitamin A carotenoids conversion factors (on a

weight basis) is 28:1 with leafy vegetables). Thus, daily consumption of 418 µg of bioavailable β-Carotene improved the lytic activity of Natural Killer cells within 15 days in average individual.

Accordingly, “LeImmune-T”, an oil extract of tomato with at least 418 microgram of bioavailable beta-carotene in 5 ml. improves/restores activity of Natural Killer Cells/Innate Immunity (the First Line Immunity) capable destroying, without the need of prior vaccination, of destroying cells infected by any virus [Novel Coronavirus (SARS-CoV-2) is a virus], bacteria and initial stage solitary cancer cells before that pathogen/cancer cell gets an opportunity to multiply to give rise to the disease”.

Regulatory position of the label claim of LeImmune-T “improves/restores activity of Natural Killer Cells/Innate Immunity capable of killing cells infected by any virus (Novel Coronavirus is a virus), bacteria and initial stage cancer cells”:

(A) Under Regulation A: This label claim complies with the sub-regulation (8)(i)(ii)(v)(v) which is recited in The Regulation A as follows:

- (8) To claim **ingredients**, nutrient or nutritional, **in respect of** an article of food for **enhanced function** and disease risk reduction, regard shall be had to-
- (i) claims that led to **ingredients** (nutrient or nutritional);
 - (ii) **available scientific literature** including official traditional texts and post market data or consumer studies or cohort or **retroactive studies based on eating pattern and health benefits, epidemiological international and national data, and other well documented data;**
 - (iii) consensual, congruent and concurrent validity studies;
 - (iv) health promotive and disease risk reduction based on proof from literature and human data of efficacy and safety of the nutrient;
 - (v) not only controlled clinical trials for efficacy and safety data; but also **nutraepidemiological** data.

(B) Under Regulation B: This label claim complies with the “other function claim” defined under definition (h) as:

(ii) **“other function claim”** that describes the **specific beneficial** effects of the consumption of foods or **their constituents, in the context of** the total diet or **normal functions or biological activities of the body, which relate to** a positive contribution to health or to **the improvement of a function** or to modifying or preserving health.”;

which is required to comply with sub-regulation 7(2) recited as follows:

“(2) Nutrient function claims and **other function claims** may be made **based on current relevant scientific substantiation and to provide sufficient evidence on the type of claimed effect and the relationship to health as recognized by generally accepted scientific review of the data** and the scientific substantiation shall be reviewed by food business operator as new knowledge becomes available and claims updated accordingly.”

“LeImmune – T” is an oil extract of tomato, which provides at least 418 µg bioavailable β-carotene in a daily dose of 5ml or less, satisfies the regulatory requirements for the claim provided above. The daily dose is indicated on the label of each batch.

Regulation (8)(i)(ii)(v)(v) recited in The Regulation of Indian Food law is reflected in the term “Significant Scientific Agreement” (SSA) provided in the guidance of US FDA on evidence based review system for the scientific evaluation of health claims available on the link <https://www.federalregister.gov/documents/2009/01/16/E9-957/guidance-for-industry-evidence-based-review-system-for-the-scientific-evaluation-of-health-claims> ; which states that:

“Significant scientific agreement refers to the extent of agreement among qualified experts in the field. On the continuum of scientific evidence that extends from very limited to inconclusive evidence, **SSA lies closer to consensus.** FDA's determination of SSA represents the agency's best judgment as to whether qualified experts would likely agree that the scientific evidence supports the substance/disease relationship that is the subject of a proposed health claim. **The SSA standard is intended to be a strong standard that provides a high level of confidence in the validity of the substance/disease relationship.** SSA means that the validity of the relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined. **SSA does not require a consensus based on unanimous and incontrovertible scientific opinion.** SSA occurs well after

the stage of emerging science, where data and information permit an inference, but before the point of unanimous agreement within the relevant scientific community that the inference is valid.”

Clinical Nutrition merits of LeImmune-T under and summary of the “Significant Scientific Agreement” that supports the merits and satisfies the requirements of regulation no. (8)(i)(ii)(v)(v) of The Regulation A as well as satisfies requirements of the current relevant scientific substantiation and to provide sufficient evidence on the type of claimed effect and the relationship to health as recognized by generally accepted scientific review of the data for “other function claim” defined under definition “h” and sub-regulation 7(2) of Regulation B i.e. “improves/restores activity of Natural Killer Cells/Innate Immunity capable of killing cells infected by any virus (Novel Coronavirus is a virus), bacteria and initial stage cancer cells” **is as follows:**

During the first critical hours and days of exposure to a new pathogen, we rely ONLY on our Innate Immune system to protect us from infection (<https://www.ncbi.nlm.nih.gov/books/NBK26846/>).

Here the term “Innate Immunity system” refers to “Natural Killer Cells mediated Innate Immune System” which is also known as “Non-specific” immunity, **which does not require a vaccination or a prior exposure to a pathogenic virus to detect a cell infected by that virus and to apoptize (kill with all the nucleic acid content) a virus infected cell.**

In elderly, Innate Immunity is compromised, but it is restored by β -carotene supplementation (Hughes,1999, Santos et al, 1996).

Clinical trial evidence shows that Bioavailability of beta carotene was better when, instead of isolated crystalline beta carotene, the same was provided through a mixed fruit and vegetable dehydrated juice Samman et al (2003).

A randomized crossover study has provided evidence that Purple Sweet Potato leaves 200g per day for 20 days increased proliferation responsiveness of PBMC, secretion of cytokines IL-2 and IL-4, **and the lytic activity of Natural Killer Cells** (Chen et al, 2005).

35g Sweet Potato leaves contain 776 μ g β -Carotene ([https://www.healthbenefitstimes.com/health-benefits-of-sweet-potato-leaves/.](https://www.healthbenefitstimes.com/health-benefits-of-sweet-potato-leaves/))

Bioavailability of beta carotene, in terms of beta carotene consumed through food sources to its conversion to Vitamin A is affected by food matrix. When beta carotene is sourced in diet from

Green Leafy Vegetables, this conversion factor by weight, in three cases is 26:1, 27:1 and 28:1 (Tang Guangwen, 2010).

To be conservative, for Sweet Potato Leaves, the factor is considered by us to be 28:1. This means, when 28mg of beta carotene is fed, one mg of Vitamin A is seen in serum arising from this feeding. Since one molecule of beta carotene makes two molecules of vitamin A, that molecule has to be the one that is bio-absorbed from the beta carotene fed through the green leafy vegetable. Hence, for bio-absorption of one molecule of beta carotene, 56 molecules of beta carotene should be fed through green leafy vegetable. Hence, in terms of bio-absorbable beta carotene the ratio is 56:1 by weight.

Chen et al. (2005) has mentioned that daily consumption of treatment group was 23.42 mg β Carotene. At bioavailable beta carotene being 56:1 by weight, the treatment group consumed $(23.42 \times 1000)/56 = 418 \mu\text{g}$ bioavailable β Carotene per day.

In conclusion, based on clinical trial of Chen et al. (2005), consumption for a human being of 79 μg of bioavailable β -Carotene shall modulate various immune functions including increased proliferation responsiveness of PBMC (peripheral blood mononuclear cell), secretion of cytokines IL-2 and IL-4, and the lytic activity of NK cells within a span of two weeks. The lytic activity of NK cells modulated Innate Immunity: the immunity which shall lyse a cell infected by ANY virus, known as well as novel; including 2019 Novel Coronavirus.

Since the active ingredient is β -Carotene, the β -Carotene sourced from any food source would give the effect of modulating Innate Immunity.

According to a clinical trial, β -carotene is absorbable only when it is transferred to fat phase of the meal (Tyssandier 2003). This reference establishes that β -carotene dissolved in fat is bio-absorbable/bio-available. Any other form of β -carotene is poorly bio-absorbable. Hence, we decided to make an oil extract of food source that has reasonably good content of β -carotene, so that whatever is the content by chemical analysis, that much shall be 100% bio-available/bio-absorbable.

NK cells have been shown to possess traits of adaptive immunity also (O'Sullivan 2015^a, O'Sullivan 2015^b).

Hence, LeImmune-T, which contains at least 418 µg of 100% Bioavailable β-Carotene in a daily dose as provided in label “improves/restores activity of Natural Killer Cells/Innate Immunity capable of killing cells infected by any virus (Novel Coronavirus is a virus), bacteria and initial stage cancer cells”.

A note on a detailed discussion on above content as well as details of supporting scientific references is attached herewith in the Annexure entitled “LeImmune-T - Support for label claim ILC” attached herewith.

There are several references which are elaborated at the end of above mentioned annexure; some of the references being from reputed and authentic sources and scientific journals such as USDA, American Institute for cancer Research, Int J Cancer., Eur J Nutr, Br J Nutr., Am J Clin Nutr., j.immuni., Innate Immun, U.S. F.D.A., Proceedings of the Nutrition Society, Expert Opinion on Biological Therapy, Advances in Immunology, Journal of Nutrition, American Society for Nutritional Sciences, Cancer Causes Control. Int J Cancer, Eur J Nutr., Journal of Epidemiology, World J Gastroenterol, Asia Pac J Clin Nutr and Am J Physiol Gastrointest Liver Physiol.

Difference between “Innate Immunity Booster” and “Immunity Booster”: Do not confuse “Innate Immunity Booster” with a large list of products which are described as “Immunity Booster”/s. “Immunity Boosters” are those products which have ingredients like zinc. Selenium, Amla etc. which improve activity of cells that mediate “Adaptive Immunity” i.e. immunity that develops after exposure to a vaccine or to the disease itself and the person recovers from the disease. Thus, such “Immune Boosters” are not useful if you are looking for protection from Novel Coronavirus infection, unless you have already developed antibodies for the Novel Coronavirus either by getting vaccinated by the vaccine for Coronavirus that is yet to come or you have got infected with the Novel Coronavirus already and either you have not developed infection because of your already strong Innate Immunity or have developed the diseases and have recovered from it.

Above established science confirms that there is only one ingredient that improves Natural Killer Cells activity, thereby improving Innate Immunity. And that is β-carotene; sourced from any food source that contains reasonable quantity of β-carotene, and its effective amount is at least 418 µg of bioavailable β-carotene in one day dose.

In other words, if an immunity booster is an “Innate Immunity Booster” only if it contain 418 µg bioavailable β-carotene in one day’s dose. It is only an “Innate Immunity Booster” that shall improve activity of the “Natural Killer Cell” and only “Natural Killer Cell” has an ability to detect a virus infected cell or an early stage cancerous cell as “non-self” and destroy it in first few hours of invasion/formation in body so that the virus or the cancer cell do/es not get opportunity to multiply and set on the disease.

LeImmune-T: the only products that has capability to bring early and conclusive end to Covid-19 Pandemic:

1. **Natural Killer Cells mediated Innate Immunity id the fundamental defense system of our body that is most difficult for the microbial pathogen to circumvent:** Thus, Innate Immunity Booster nips out the problem in the bud itself; and in the fight against Novel Coronavirus, if Innate Immunity Booster is given to ALL immune-compromised persons, it not only “improves/restores activity of Natural Killer Cells/Innate Immunity capable of killing cells infected by any virus (Novel Coronavirus is a virus), bacteria and initial stage cancer cells”; but also helps in breaking the chain of infection because it is only the innate-compromised people that have high risk of falling prey to the infection; and if they again become immune, the chain will get broken very easily.
2. **Sanitation, face masks and social distancing are relevant only until a small mistake is made in their use:**
 - a. Sanitation, face masks and social distancing are very important, However, anybody can make a small mistake inadvertently in their use; and that opportunity to the pathogen of entry in the body is enough to get disease, if Innate Immunity is not optimum. This can happen even with most meticulous persons, which is shown by infection of a significant number of policemen, doctors, nurses, hospital. Staff, central and state ministers known for their meticulousness. Had they had their Natural Killer Cells activity at optimum, they would not have got the disease at all.
 - b. Impracticality of education on and getting compliance of people on social distancing has been proven by the fact that even after prolonged lock-down, there is no flattening of the infections and downward rate of infection is not even within sight; every day’s number of fresh cases is setting a new record of infections in 24 hours and India is required to open up under a pressure that economy has to start working. Hence, there is something that is not being taken

into consideration; and that is Natural Killer Cells mediated Innate Immunity management.

3. **Low mortality rate should not lead to complacency – recovered persons have been seen to carry on several problems even after recover affecting their quality of life:** It is most important to try best to avoid getting sick at all because it has been seen that even after getting corona-negative, there are several problems and disabilities that persist adversely affecting quality of life, and it is not known so far, how long they will persist.
4. **Vaccine and its limitations in the context of Novel Coronavirus:** Vaccine is important because it shall have antibodies specific for the Coronavirus. However, immunity developed from the vaccine may not live longer than 3 months. Thus Innate Immunity Booster – **LeImmune-T would be needed prior to arrival of vaccine as well as after vaccination:**
 - a. **An alarmingly short duration of protective immunity:** Researchers from the University of Amsterdam tested 10 men for four coronaviruses regularly over the course of 35 years. The four coronaviruses cause the common cold and research said there was 'an alarmingly short duration of protective immunity', The Times reported. People may only be immune to coronaviruses for six months, ----- (<https://www.msn.com/en-in/health/familyhealth/immunity-to-coronavirus-could-only-last-six-months-study-finds-casting-fresh-doubt-on-ministers-plans-to-give-survivors-immunity-passports/ar-BB14u7Ya?ocid=spartanntp>).
 - b. **Steep drop in patients' antibody levels three months after the infection:** A longitudinal study by the researchers from King's College London — first reported by The Guardian on Sunday — has suggested that immunity to Covid-19 might be lost in months. The suggestion is based on a steep drop in patients' antibody levels three months after the infection. The researchers analyzed the immune response of 90 recovered Covid-19 patients and healthcare workers. In their study, which is not yet peer-reviewed, they found that antibodies that specifically help in neutralizing the coronavirus SARS-CoV-2 decreased 2-23-fold during an 18-65 day follow-up period. This is similar to the decrease in antibodies seen in seasonal coronaviruses associated with the common cold. (<https://www.msn.com/en-in/news/in-depth/explained-how-immunity-is-developed/ar-BB16K4xl?ocid=msedgntp>).

c. **Official acknowledgement of American healthcare organization that Novel Coronavirus adaptive immunity lasts for 3 months only:**

The Centers for Disease Control and Prevention (CDC) has been the institution Americans have consistently turned to for guidance throughout the COVID-19 pandemic. The updated guidance on quarantine protocols is released at the beginning of August states: "People who have tested positive for COVID-19 do not need to quarantine or get tested again for up to three months as long as they do not develop symptoms again," implying some level of immunity during that period of time as a result of antibodies. (<https://www.msn.com/en-in/health/medical/the-cdc-just-made-a-major-reveal-with-this-new-covid-guideline/ar-BB17YJHC?li=AAggbRN&ocid=wispr>).

- i. This also implies that three months after testing positive, their Adaptive Immunity on account of antibodies developed in this body shall remain effective only until three months.

d. **Life of Adaptive Immunity that may develop from a vaccine:** It is clear that vaccine is developed from a small part of the Novel Coronavirus; and it cannot be expected to have immunity lasting for more period than the immunity developing from the original Novel Coronavirus.

e. **Lower response to vaccines in adults, smokers and co-morbid persons:** Lower response to vaccines have been observed in increasing aged adults, male, BMI ≥ 25 , smoking and concomitant disease. The prospective vaccine/s on Novel Coronavirus is/are not likely to be an exception. Remedy on this problem is: more vaccine doses, supplemental/additional strengthening immunity should be focused on this specific population (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4914839/>). This "supplemental/additional strengthening immunity" is available from a Natural Killer Cell mediated Innate Immunity Booster: the **LeImmune-T**.

In conclusion: LeImmune-T would be needed prior to arrival of vaccine as well as after vaccination for comprehensive and best benefits for controlling the pandemic.

LeImmune-T: for stability of economy of commercial establishments and the Country:

Withdrawal of lock-down in a situation when fresh cases are still popping up, and/or every day

the number of infected people is increasing, is putting immune-compromised people at far greater risk than the first day of start of lock-down.

Hence, particularly for offices and industrial establishments having large number of employees, if after re-start of work after lockdown is withdrawn is to be protected from potential re-imposition of repeat lock-down, ideal way is to ensure that every individual in the society consumes LeImmune-T. However, in practical circumstances, until this product becomes available to each and everybody, prioritization may be needed to be made. First priority should be to persons with highest risk of infection and their family members, which includes is to doctors, nurses, ward-boys, sanitation employees of Covid-Hospital, policemen working in high risk areas, and all professionals whose profession is connected to high infection risk areas and Innate Immunity-compromised persons (Type-II diabetics, hypertensives, heart diseased, cancer patients, Chronic-Kidney-Disease patients of all ages; and elderly persons of 50 years age and above). Next in list should be those who are engaged in high physical strain duties and duties in shifts in factories and their family members. Thereafter should follow all remaining population.

In industrial areas, all industries need to be covered under access to LeImmune so that there is reduction in risk of entire Industrial area getting closed down once again if number of cases increase with withdrawal of lock-down. It is a matter of fact that current surge in number of cases in India is attributed to the limited relaxation provided at the beginning of fourth phase of lock-down. It is now known that relaxations are not cautiously used by a significant number of people. Hence, Innate Immunity improvement route by the Innate Immunity boosters described here may prove to be more practical route for a safer withdrawal.

Restoration of Innate Immunity from its depressed level does take some time, a week or two. Ideally, these Innate Immunity Boosters should be started being provided one or two weeks prior to the relaxation for best effect; so that when the normal working starts, the people whose Immunity is compromised today, shall have their Innate Immunity restored to a great extent.

With protection of innate Immunity compromised employees and Innate Immunity compromised family members of all employees is required to avoid further economic losses. **Expenditure on Innate Immunity Booster for these people shall be a far less investment as compared to economic losses, if re-imposition of Lock-down becomes necessary. It may be desirable to propose this measure for all industries in an Industrial Area so that the entire Industrial Area will become safe. For small industries in that industrial area who may not be able to afford such measures, bigger industries in that area may consider supporting**

employees and their families of smaller industries also under Corporate Social Responsibility. Additionally, it will help in breaking chain of infection and development of “Herd Immunity” in a very safe way; and eradication of Novel Coronavirus; with or without the vaccine.

It is also not certain that the Novel Coronavirus may not mutate. If it does mutate and if new strain/s is/are more virulent and the currently in-process vaccines do not work against them, the currently in-process vaccines or Adaptive immunity developed against them may have to be supplemented with an Innate Immunity Booster, so that the mutated Coronavirus strain circulating in the population will also get covered in this dual approach.

WHO has repeatedly stressed that very little is known about this Novel Coronavirus; and it has come to stay for a long time; and worst is yet to come. LeImmune-T shall provide a pro-active and strong support to any action against such a possibility.

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