

DENVAX™

(AUTOLOGOUS DENDRITIC CELL CANCER VACCINE)

MONOGRAPH

Amount 10 ml, packed in 2 vials.

Stored at 4°-8°.

To be used within 30 hours of packaging.



Nurturing Cells for Lives

www.dendriticcellresearch.com

INSTITUTE OF CELLULAR THERAPIES PVT. LTD.

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India

Date: 1st May 2008

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DENVAX™
AUTOLOGOUS DENDRITIC CELL CANCER VACCINE

Part I HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

ROUTE OF ADMINISTRATION	DOSAGE FORM	NON MEDICINAL INGREDIENTS
Intravenous	Total 10.0 ml in 2 vials	No known clinically relevant non-medicinal ingredients

INDICATIONS AND CLINICAL USE

Denvax is comprised of mature Dendritic cells given along with various cytokines. The source of dendritic cells is patient's own mononuclear cells transformed into cancer-specific dendritic cells by culturing them in the laboratory at ICT. Denvax is indicated as adjunctive immunological therapy for the management of patients in stage IV cancers (detailed later) who are not satisfactorily controlled by conventional chemotherapy, surgery and radiotherapy. This therapy is proposed to be useful in delaying cancer progression in treated patients of solid cancers, non-Hodgkin's lymphoma and multiple myeloma.

Geriatrics (>65 years of age)

Systemic studies in geriatrics patients have been conducted and the product Denvax is found safe. (See **Warnings and Precautions** also)

Pediatrics (<16 years of age)

The safety and efficacy in patients less than 16 years of age has not been established. (See **Warnings and Precautions** also)

CONTRAINDICATIONS

Denvax is contraindicated in patients who have demonstrated hypersensitivity to the dendritic cells or to any of the components of the formulation.

WARNINGS AND PRECAUTIONS

General

There are no general warnings with Denvax in all malignancies, of any stage.

Discontinuation of Treatment with Denvax

The treatment can be stopped abruptly without causing any known adverse effects.

Concomitant Use with Chemotherapy/ Radiation

Denvax can be concomitantly given with chemotherapy or radiation therapy but should preferably be given before or after 72 hrs of chemotherapy and before or after 24 hrs of radiation. During this period the dendritic cells effectively settle down in lymph nodes and generate T and B cell immunity for generating effective anti-cancer immunology.

Concomitant Use with Steroid

Concomitant use of steroids does not hamper the effect of Denvax.

Carcinogenesis and Mutagenesis

The constituents of Denvax do not contain any live malignant cells. It has zero potential to induce malignancy into the patient. Denvax does not promote new cancer formation or aggravate the existing cancer.

Dependence and Tolerance

There is no evidence of dependence and tolerance with Denvax therapy. Discontinuing Denvax treatment will not affect normal immuno-physiology of the recipient. It does not enhance the chances of cancer progression.

Special Precautions

Pregnant Women

There is no adequate and well-controlled study to establish the safety and efficacy of Denvax therapy in pregnant females. Denvax should not be given to pregnant females as its humoral immune response can break placental barrier and has the potential to affect fetal development.

Nursing Women There are no evidences to prove safety of Denvax therapy in nursing mothers. It has not been used in pregnant or nursing mothers, and should be used ONLY if absolutely required.

Geriatrics Denvax therapy is safe to be given to the elderly (>65years of age) and is well tolerated. Minor adverse events reported with adults and geriatric population remains in the same ratio.

Monitoring And Laboratory Tests

Clinical data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Denvax. The Denvax treatment can even be used in association with other immune regulatory drugs like Dexamethasone and Prednisolone is essential. Cellular immune responses, mainstream of cancer cell therapy will remain functional while generated humoral responses will be hampered.

ADVERSE REACTIONS

Commonly Observed Adverse Reactions

The most commonly observed adverse events associated with the usage of Denvax are fever, eliciting within half to two hours of infusion; fever with chills and rigors in the same time period; lethargy; somnolence and fatigue. Vomiting remains the most common adverse reaction and Denvax is ideally given along with intravenous anti-emetics.

Adverse Events leading to Discontinuation

There are no absolute contraindications to Denvax therapy. In a few patients of multiple myeloma, hematuria was reported with first and second dose of therapy along with fever, chills and rigor. The hematuria presented itself in first stream of urine and subsided without any intervention. Occasional patients of osteosarcoma reported increase in pain at the site of disease for 24 to 48 hrs. Later, it resulted in feeling of low pain threshold than pain present before Denvax treatment plan.

Clinical Trials Adverse Drug Reactions

Because clinical trials were conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Incidence in Controlled Clinical Trials

Adults

Multiple doses of Denvax were administered to 300 subjects with cancer at various stages of clinical and pathological stages. No alarming incident was reported in patients receiving Denvax.

Table I

Treatment-Emergent Adverse Events Incidence in Non Placebo-Controlled Add-On Trials
(Events in at Least 1% of Denvax Patients)

	Denvax n=300 (%)
Body as a whole	
Fatigue	36.0
Weight Increase (2 months)	46.0
Back Pain	1.2
Peripheral Edema	1.7
Cardiovascular	
Vasodilatation	8.0
Digestive system	
Dyspepsia	13
Mouth or Throat Dry	1.4
Constipation	1.5
Dental Abnormalities	1.2
Increased Appetite	1.4
Hematological and Lymphatic System	
Leukopenia	1.1
Leukocytosis	26
Musculoskeletal	
Myalgia	2.0
Fracture	0.8
Nervous System	
Somnolence	3.2
Dizziness	4.6
Ataxia	2.0
Nystagmus	0.9
Tremor	1.3
Nervousness	1.2
Depression	1.6
Amnesia	0.8

Dose Related Treatment Emergent Adverse Effects

Weekly administration of Denvax was well tolerated in certain patients. There is no dose-related emergence of adverse effects.

Supply of Denvax is restricted to a single dose per schedule and chances of over dosage in a single day are impossible.

Other Adverse Events Observed in All Clinical Trials

Adverse events that occurred in at least 1% of the 300 individuals who participated in study group, are listed below. During these trials, the clinical investigators used terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 300 patients exposed to Denvax who experienced an event of the type cited on at least one occasion while receiving Denvax. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the biological therapy.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/250 patients; rare events are those occurring in fewer than 1/>250 patients.

Body As A Whole: *Frequent:* asthenia, malaise; *Infrequent:* allergy, redness and itch at the site of infusion, weight no effect, chill occasional; *Rare:* strange feelings, lassitude, weakness and feeling of ill health.

Cardiovascular System: *Frequent:* Blood pressure –transient hypotension; *Infrequent:* sustained hypotension, palpitation, tachycardia; *Rare:* heart failure, thrombophlebitis, deep thrombophlebitis, bradycardia, premature atrial contraction, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, and pericarditis.

Digestive System: *Frequent:* anorexia, flatulence; *Infrequent:* thirst, stomatitis, increased salivation, gastroenteritis, peptic ulcer; *Rare:* dysphagia, pancreatitis, colitis, esophagitis, and esophageal spasm.

Endocrine System: *Rare:* hyperthyroid, hypothyroid, goiter, ovarian failure, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent:* WBC count increased, mild anemia, lymphadenopathy; *Infrequent:* moderate anemia, thrombocytopenia, localized lymphadenopathy; *Rare:* lymphocytosis, lymphadenopathy at multiple sites.

Musculoskeletal System: *Frequent:* arthralgia, increased pain intensity at the site of disease; *Infrequent:* positive Romberg test; *Rare:* sustained pain intensity.

Nervous System: Frequent: Nil; *Infrequent:* syncope, dreaming abnormal, aphasia, paresis, stupor, decreased position sense, euphoria, feeling high; *Rare:* encephalopathy, subdued temperament, fine motor control disorder, hyperesthesia, hypokinesia,

Respiratory System: *Infrequent:* dyspnea, apnea; *Rare:* mucositis, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation.

Dermatological: *Infrequent:* eczema, increased sweating, urticaria, seborrhea, cyst, herpes simplex; *Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, desquamation, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence; *Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency.

Post-Market Adverse Drug Reactions

Denvax has not yet been made available in multi-centers. Its adverse reactions can be e- mailed to info@dendriticcellresearch.com or sent by regular mail to ICT Pvt. Ltd. J-3/Sector41, Noida. Pin 201303.

DRUG INTERACTIONS

Overview

Denvax is not metabolized to a significant extent in humans and does not interfere with the metabolism of commonly administered chemotherapy drugs. There have been few drug interactions described in which the pharmacokinetics of Denvax or other co-administered drugs were affected to an appreciable extent.

Drug-Drug Interactions

The drug interaction data described in this subsection were obtained from studies involving healthy adults and adult patients with cancer.

Chemotherapy drugs

There is no interaction between Denvax and other chemotherapy drugs used concomitantly. Consequently, Denvax may be used in combination with other commonly used anticancer drugs without concern for alteration of the plasma concentrations of Denvax or the other anticancer drugs.

Drug-Food Interactions

Denvax may be given intravenously, with or without food.

Drug-Herb Interactions

Interaction with herbal products has not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Because Denvax consists of live Dendritic cells along with cytokines (IL-2, IL-4, G-CSF, GM-CSF, TNF, IL-12) dosage adjustments are not recommended for patients with renal impairment (including elderly patients with declining renal function) and patients with liver disease. In patients having serum bilirubin more than 5mg%, Denvax has no clinical benefit.

Adults

Denvax is supplied in two vials (total 10.0 ml) and given intravenously by mixing contents of both vials into 100 ml of Dextrose Normal Saline (DNS) solution. 4 mg of Ondansetron is given intravenously prior to Denvax infusion, and is completed within 30 minutes. 0.1 ml of test dose should be given on volar aspect of forearm and usual reactions of hypersensitivity like erythema, induration and itching are noted for 15 minutes. This test dose can be ignored in subsequent administrations.

Dosage

The initial dose is one million cells in 10.0 ml of Denvax preparation. Subsequent doses may be adjusted in accordance with the response and tolerance of the patient.

Frequency

Initially, three Denvax doses are to be given at three weeks interval, each. Then onwards it is given at 4 weeks interval. Additional doses on monthly basis can be given indefinitely without any added adverse effects or tolerance. In palliative care settings, dosage range has been found to be effective at monthly intervals.

No clinical benefit is observed in patients who were given weekly doses as compared to patients receiving doses at every 21 days, or at monthly intervals. Increasing the frequency has not shown to add to clinical response.

Maintenance

Maintenance doses of Denvax are given at monthly intervals. As there are no drug interactions of Denvax with commonly used chemotherapy drugs, the therapy can be continued for life in palliative care settings.

Overdosage

Overdosage with Denvax therapy is a rare possibility as Denvax is supplied under supervision at timely schedules only.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Denvax comprises of 60 –70% live, mature dendritic cells along with monocyte growth medium, including cytokines namely IL-2, IL-4, IL-12, IL-6, GM-CSF, G-CSF and TNF-alpha in various proportions. Dendritic cells, obtained from patient's peripheral blood mononuclear cells (CD 14+), are cultured *ex vivo* on cell-surface treated plates, in the presence of cytokines and nutritional media. On the 6th day of culture, these cells are matured in the presence of tumor lysate (antigenic repertoire). These mature dendritic cells are harvested on the 8th day of culture, for administration. Denvax (amounting to 10.0 ml) is administered intravenously as infusion in 100.0 ml DNS.

The cell medium is assessed for aerobic, anaerobic and mycoplasma contamination by routine culture and ELISA techniques. Dendritic cells are counted by Trypan blue exclusion staining for viability and is 90% at the time of packaging. CD83, CD86 and DRII marker studies are done to confirm maturation response.

Upon administration, studies suggest that dendritic cells along with chemokines are transported to lymph nodes within half an hour of infusion. Due to their dendritic processes, dendritic cells attract naïve T cells on their surfaces resulting in their transformation to committed T lymphocytes. Each dendritic cell has the ability to target up to 5000 T-cells per hour and generate tremendous anti-cancer immunity. B cell activation albeit with low potential also takes place by dendritic cell activation, resulting in production of antibodies against cancer cells. Committed T cells eventually are released in circulatory system and target micro-metastases attacking and killing them. Cancer progression is stopped or delayed resulting in clinical response. Humoral immune response may affect and contribute towards lowering of symptoms of nausea, cachexia and pain associated with advanced disease. The identity of humoral immunity remains to be elucidated.

Pharmacokinetics

All pharmacological actions following Denvax administration are due to the activity of the adoptive immunology by recruiting T and B cells; dendritic cells are neither metabolized in liver nor kidney but accumulated in lymph nodes. Deeper lymph nodes around tumor tissue often become prominent after Denvax treatment.

Absorption

Following i.v. infusion of Denvax, dendritic cells reach to lymph nodes within half to one hour of completion of infusion.

Distribution

Dendritic cells are carried to deeper lymph nodes and are not found in peripheral circulation after 2 hours of infusion.

Metabolism

The cytokines used for the preparation of Denvax are metabolized along with normal metabolic responses; the major component of Denvax is autologous dendritic cell and this does not come under preview of metabolism.

Excretion

Denvax is a cell preparation and is not excreted via the excretory mechanisms.

Tumor Specific Immune Response: *In vitro* IFN- γ Assay

To assess the potential of Denvax to generate a tumor-specific immune response, an *in vitro* assay IFN- γ is performed to determine intracellular IFN- γ production in peripheral T cells. IFN- γ production in CD3⁺ lymphocytes is assessed by immuno-florescence. After co-culture with mature monocyte-derived dendritic cells the expression of CD69 and IFN- γ in CD3⁺ cells, which were not stimulated with PMA or ionomycin, was significantly higher in cells obtained after 3rd dose of vaccination than in the cells obtained before first vaccination. On stimulation with PMA and ionomycin during the co-culture with mature monocyte-derived dendritic cells, the expression of IFN- γ was significantly higher in DC/T4 than in DC/T0 cells, whereas expression of CD69 revealed no difference. T0 and T4 cells, with and without lysates pulsing, were used as controls, and they did not exhibit strong expression of either CD69 or intracellular IFN- γ .

Bio-equivalence of Dosage Forms

Denvax is supplied in two vials having slight variation in constituents and is packed so to create the potency of two vials as separate units. Both vials are finally mixed in infusion at the time of delivery. The vials are to be stored between 4^o-8^oC and have shelf life of 24-30 hours at this temperature.

STORAGE AND STABILITY

Vials: Store at 4^o-8 C

Viability: Viable 30 hours from package time till infusion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Available as a light-pink to pink colored turbid solution (turbidity visible on shaking) packed in two vials, used as single dose, to be given intravenously only. To be diluted in

100 ml of DNS/NS for infusion.

Special Precaution

Injection Ondansetron (4mg) is to be given prior to infusion therapy.

Dosage Forms

For Palliative Care Settings: To be given every 21 days for three doses. To be given thereafter as monthly dose.

Cancer

Breast Cancer including ER/PR/Her2neu negative cancer

Hepatocellular Carcinoma

Gallbladder Cancer

Ovarian Carcinoma

Head and Neck Cancer

Non-Small Cell Lung Cancer

Prostate Cancer

Renal Cell Carcinoma including metastatic disease

Thyroid Cancer

Non-Hodgkin's Lymphoma including CD20 negative cancer

Multiple Myeloma

Osteosarcoma

Chondrosarcoma

Soft tissue sarcoma

The Denvax treatment can be given in two settings

a) Palliative Care;

b) Preventing Relapses.

Palliative care settings: Denvax treatment is given on monthly basis and should continue if clinical benefits are appreciable. In clinical trials, it has been seen that precisely three doses of Denvax treatment will produce a cumulative effect and can be guidance for efficacy of treatment and its continuation.

Preventing relapse: In patients achieving CR (complete response) by conventional treatment, Denvax can be given for three months as monthly dose. The relapse rate decreases considerably. Denvax therapy can be extended up to 6 months to 1 year for further reducing the cancer relapse rate to 90%, as compared to historical controls. In highly malignant cancers, giving Denvax treatment for prolonged periods even up to 3 years prevents relapse. Cancers like hepato-biliary cancers, operated gallbladder cancer, glioma multiforme, NSCCL, Osteosarcoma and Head and Neck cancer have shown complete remission with prolonged treatment, in pilot studies done under controlled conditions.

PART II - SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug

Denvax contains no active drug component. Denvax is autologous dendritic cell vaccine. It contains one million (+/- 2%) dendritic cells of which 70% (+/- 2%) are mature dendritic cells along with IL-2, IL-4, IL-6, IL-12, GM-CSF, G-CSF, TNF-alpha. During cell culture, IL-4 and GM-CSF are added for transforming mononuclear cells (CD14+) into mature dendritic cells (CD83, CD86, DEC205 positive).

Denvax is composed of patient's own mononuclear cells extracted from peripheral blood. Apheresis, a procedure to draw CD14+ cells is not mandatory for dendritic cell culture. The patient's total leucocytes count signifies the amount of whole blood required for making one Denvax dose.

Cancer and The Immune System

Cancer is caused by mutations. It could be familial, environmental or of unknown etiology. During cancer development, self-cells become non-self cells. Mutating cells acquire a shield mechanism for evading immune attack. They may hide their antigenic nature by topographic shield or produce IL-10 for negative chemotaxis or develop an unknown hidden mechanism to evade their arrest. Once the cancer cells start proliferating, the immune mechanisms become so ineffective, that it actually starts contributing towards cancer proliferation. At this stage, cancer develops rapidly and profoundly. Otherwise cancer growth may become slower or delayed if immune system is still able to check it irregularly.

The deranged immune system can be corrected passively by chemotherapy and/or surgery. If it happens this way, cancer patients become cancer survivors, or otherwise, cancer returns with vengeance making itself more resistant to chemotherapeutic drugs used earlier.

Normal anti-cancer immunology can be enhanced in laboratory also. The process is similar to the normal immune process except that it is being done in controlled condition in cell surface treated petri-plates.

The peripheral blood mononuclear cells are isolated from peripheral blood and cultured with specific cytokines for changing their morphology to dendritic cells. The dendritic cells are given a basic information of cancer type, by adding tumor associated antigens (TAA) and tumor specific antigens (TSA) to the culture plates. Dendritic cells recognize the antigen feedback and respond by producing specific antigenic peptides (representation) on their surfaces. These mature dendritic cells are re-infused to the same patient after eight days of culture for generating specific anti-cancer immunity. After infusion, these dendritic cells along with specific cytokines are carried to various lymph nodes and station themselves in these lymph nodes. They start their physiological action on naïve T cells. Upon physiological contact with dendrites of DC, T cells become committed in the vicinity of dendritic cells. Each dendritic cell is having a potential to mature 3000-5000 T cells/hour. Dendritic cell survives on an average of 3 weeks to months, and during this period it is able to selectively transform trillions of T cells. The robust anticancer immunology doesn't allow new malignant cells to grow and stops or delays tumor progression. Dendritic cells leading to IL-12 and TNF-alpha generation also generate humeral immunology helpful in reducing cachexia.

TOXICOLOGY

No acute toxicity has been reported from 1600 doses given to 300 patients in different stages of cancer.

Chronic Toxicity

For systemic toxicity the National Cancer Toxicity scale was used, given below in Table 2.

Table 2. NCI (National Cancer Institute) Common Toxicity Criteria

Category	Toxicity	Grade0	Grade1	Grade2	Grade3	Grade4
NEUROLOGICAL	Cerebellar	None	Slight incoordination, dysdiadokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	cerebellar necrosis
NEUROLOGICAL	Mood	No change	Mild anxiety, depression	Moderate anxiety, depression	Severe anxiety, depression	Suicidal ideation
NEUROLOGICAL	Headache	None	Mild	Moderate or severe, transient	Severe, unrelenting	--
NEUROLOGICAL	Constipation	None or no change	Mild	Moderate	Severe	Ileus > 96 hrs
NEUROLOGICAL	Hearing	None or no change	Asymptomatic hearing loss on audiometry only	Tinnitus	Hearing loss interfering with function, correctable with aid	Deafness not correctable
NEUROLOGICAL	Vision	None or no change	--	--	Symptomatic subtotal loss	Blindness
SKIN	SKIN	None or no	Scattered macular or	Scattered macular or papular rash or	Generalized symptomatic	Exfoliative or ulcerating dermatitis

		change	papular rash or erythema that is asymptomatic	erythema with pruritis or other symptoms	macular, papular, or vesicular rash	
ALLERGY	ALLERGY	None	Transient rash, drug fever <38°	Urticaria, drug fever = 38° mild bronchospasm	Serum sickness, bronchospasm requiring parenteral meds	Anaphylaxis
FEVER/NO INFECTION	FEVER/NO INFECTION	None	37.1 - 38.0°	38.1 - 40.0°	>40° for < 24 hrs	>40° for > 24 hrs or fever accompanied by hypotension
TISSUE	LOCAL	None	Pain	Pain & swelling with inflammation or phlebitis	Ulceration	Plastic surgery indicated
WEIGHT GAIN/LOSS	WEIGHT GAIN/LOSS	< 5.0%	5.0 - 9.9%	10.0 - 19.9%	>20%	--
METABOLIC	Hyperglycemia	< 116	116 - 160	161 - 250	251 - 500	>500 or ketoacidosis
METABOLIC	Hypoglycemia	>64	55 - 64	40 - 54	30 - 39	< 30
METABOLIC	Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 x N	>5.1 x N
METABOLIC	Hypercalcemia	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	>13.5
METABOLIC	Hypocalcemia	>8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	< 6.0
METABOLIC	Hypomagnesemia	>1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	< 0.5
PULMONARY	Pulmonary	None or no change	Asymptomatic with abnl PFT's	Dyspnea on significant exertion	Dyspnea with normal activity	Dyspnea at rest
CARDIAC	Dysrhythmias	None	Asymptomatic, transient requires no Rx.	Recurrent or persistent Requires no Rx.	Requires Rx.	Requires monitoring; or hypotension; or vent. tachycardia/fibrillation
CARDIAC	Function	WNL	Asymptomatic, resting ejection fraction Ø'd by <20% of baseline	Asymptomatic, resting ejection fraction Ø'd by >20% of baseline	Mild CHF, responds to Rx.	Severe, refractory CHF
CARDIAC	Ischemia	None	Nonspecific T-wave flattening	Asymptomatic, ST/T wave changes suggesting ischemia	Angina without evidence for infarction	Acute myocardial infarction
CARDIAC	Pericardial	None	Asymptomatic effusion, no Rx. required	Pericarditis - rub, chest pain, ECG changes	Symptomatic effusion, drainage required	Tamponade; drainage urgently required
BLOOD PRESSURE	Hypertension	None or no change	Asymptomatic, transient _ by >20 mm (D) or to >150/100 if previously WNL. No Rx.	Recurrent/persistent _ by >20 mm (D) or to >150/100 if previously WNL. No Rx.	Requires Rx.	Hypertensive crisis
BLOOD PRESSURE	Hypotension	None or no change	Changes not requiring Rx. (includes transient orthostatic hypotension)	Requires fluids or other Rx. but not hospitalized	Requires Rx. and hospitalization; resolves within	Requires therapy and hospitalization for >48 h after stopping agent
NEUROLOGICAL	Sensory	None or no change	Mild paresthesias, loss of deep tendon reflexes	Mild or moderate objective sensory loss; moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	--
NEUROLOGICAL	Motor	None or no change	Subjective weakness, no objective	Mild objective weakness, no significant loss of	Objective weakness with loss of function	Paralysis

			findings	function		
BLOOD/BONE MARROW	WBC (x1000/mm3)	>4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
BLOOD/BONE MARROW	PLT (x1000/mm3)	WNL	75.0-WNL	50.0-74.9	25.0-49.9	< 25.0
BLOOD/BONE MARROW	Hgb (gm/dl)	WNL	10.0-WNL	8.0-10.0	6.5-7.9	< 6.5
BLOOD/BONE MARROW	ANC (x1000/mm3)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
BLOOD/BONE MARROW	Lymph (x1000/mm3)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
HEMORRHAGE	Hemorrhage	None	Mild, no Tx. per episode	Gross, 1-2 units Tx. per episode	Gross, 3-4 units Tx. per episode	Massive, >4 units Tx. per episode
INFECTION	Infection	None	Mild	Moderate	Severe	Life-threatening
GASTROINTESTINAL	Nausea	None	Able to eat	Able to eat reasonable intake	Unable to eat Ø intake	--
GASTROINTESTINAL	Vomiting	None	1 emesis/24 h	2-5 emeses/24 h	6-10 emeses/24 h	>10 emeses/24 h or parenteral support
GASTROINTESTINAL	Diarrhea	None	_ of 2-3 stools/d over pre-Rx	_ of 4-6 stools/d moderate cramping nocturnal stools	_ of 7-9 stools/d severe cramping incontinence	_ of >10 stools/d parenteral support grossly bloody stools
GASTROINTESTINAL	Stomatitis	None	Erythema, painless ulcers, mild soreness	Painful erythema, edema, ulcers can eat	Painful erythema, edema, ulcers cannot eat	Parenteral or enteral support
HEPATIC	Bilirubin	WNL	--	< 1.5 x N	1.5-3.0 x N	>3.0 x N
HEPATIC	SGOT/SGPT	WNL	< 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HEPATIC	Alk Phos/5'Nucleotidase	WNL	< 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HEPATIC	Clinical	--	--	--	Precoma	Hepatic coma
RENAL/BLADDER	Creatinine	WNL	< 1.5 x N	1.5-3.0 x N	3.1-6.0 x N	>6.0 x N
RENAL/BLADDER	Proteinuria	No change	1+ or <0.3 gm% (<3 gm/L)	2-3+ or 0.3-1.0 gm% (3-10 gm/L)	4+ or >1.0 gm% (>10 gm/L)	Nephrotic syndrome
RENAL/BLADDER	Hematuria	Neg.	Microscopic	Gross, no clots	Gross + clots	Requires Tx.
ALOPECIA	Alopecia	No loss	Mild hair loss	Near or total hair loss	--	--
NEUROLOGICAL	Cortical	None	Mild somnolence, agitation	Moderate somnolence, agitation	Severe somnolence, agitation, confusion, disorientation, hallucinations	Coma, seizures, toxic psychosis
COAGULATION	Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.5 x N	0.49 - 0.25 x N	< 0.24 x N
COAGULATION	Protrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.5 x N	1.51 - 2.0 x N	>2.0 x N
COAGULATION	Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.0 x N	>3.0 x N

For local vaccine toxicities, the following scale was used:
Grade 1, erythema and induration <20 mm
Grade 2, erythema and induration ≥20 mm, without ulceration
Grade 3, ulceration and painful adenopathy
Grade 4, permanent dysfunction related to local toxicity

Carcinogenesis and Mutagenesis

Patients receiving more than 12 doses of Denvax have not reported any new cancer formation after discontinuation of Denvax for more than 24 months.

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PART III

CONSUMER INFORMATION

This part of the Denvax Monograph is designed specifically for consumers. This includes a summary and will not tell everything about Denvax. You may contact your doctor or ICT Pvt. Ltd. at J 3 Sector 41, Noida, if you have any questions about Denvax. Please read the instructions carefully before you start to take your Denvax cell therapy. For further information or advice, please ask your doctor or write to us.

A brief summary about DENVAX

Denvax is autologous cell treatment in cancer. Here patient's cells (taken from 20 ml peripheral blood) are cultured and transformed into dendritic cells (cancer-fighting cells). The cells are cultured by *ex vivo* technology in 8 days and re-infused into the same patient. The treatment is part of customized targeted therapies. The dendritic cells once inside the body generate robust immunology to fight cancer. Denvax is intended to use as adjuvant therapy, and in no way is a substitute to conventional treatment. Denvax can be given under the supervision of your doctor, who can monitor the treatment outcome.

The best stage to use Denvax

Denvax being a cell-based therapy works best when the tumor load is minimal, i.e. after surgery or when the patient is in remission or in complete response phase. Given in zero tumor loads it is found to prevent or delay relapse. Denvax used concomitantly with the existing chemotherapy/radiation therapy plan, aids in enhancing the clinical outcome.

Cancers

Below is a list of cancer which have shown a definite response:

Brain cancer	Lung (NSCCL)
Breast cancer	Renal cell carcinoma
Bone cancer	Ovarian cancer
Gallbladder cancer	Head and neck cancer
Hepatocellular cancer	Sarcoma
Pancreatic cancer	Testicular cancer
Prostate cancer	Uterine cancer
Multiple myeloma	Cholangiocarcinoma
Lymphoma	Colon cancer
Stomach cancer	

Note: Denvax has not proven to be of benefit in Leukemias. If your cancer is not listed in the above-mentioned table, you may still benefit from this treatment. You may consult our doctors at ICT Pvt. Ltd., Noida, or email us at info@dendriticcellresearch.com.

When can Denvax be used?

As Palliative Treatment

DENVAX aids in reducing cancer morbidity and improves quality of life. Clinical studies comparing outcome in Group A patients receiving conventional treatment and Group B patients put on both conventional and Denvax, showed better performance in Group B in relation to time to disease progression, improved quality of life and extension of life.

As Protection From Future Relapses

Denvax taken after completion of conventional therapy helps in reducing relapse rate. A comparative study in two groups IA AND IB- showed protection from relapse in Group IB (on 3-6 monthly Denvax treatment after the completion of conventional treatment plan) patients as opposed to Group IA patients receiving no treatment after completion of conventional treatment plan.

How is Denvax taken?

Your personalized Denvax shall reach you on the date assigned to you, in a cold chain carrier. Denvax is a pink colored solution. Please check your name and identification code given. It will reach you after 8 days' of blood collection; for example, if blood was drawn on Monday, your Denvax will be ready to be administered on the next Monday. Denvax is administered intravenously as infusion in 100 ml dextrose normal saline (DNS) along with an injection of Ondansetron (4 mg), an anti-emetic.

Dietary Advice

There are no specific dietary recommendations, before or after Denvax therapy.

Active medicinal ingredients in Denvax

There are no active medicinal ingredients present in Denvax. It contains your own mature dendritic cells along with cytokines (substances necessary for cell development).

What are the important non-medicinal ingredients present in Denvax

No known non-medicinal ingredients in the form of stabilizers including alum, starch, gelatin, talk, silicon dioxide, titanium dioxide commonly used in 'drugs' are present in Denvax.

Side Effects Management

Common side effects are fever, with or without chills and rigors, and lethargy. Fever may appear in 30 minutes of vaccine administration and may last for 24 to 48 hrs. Fever subsides by taking a tablet of paracetamol (acetaminophen).

Feeling of nausea or vomiting may remain for initial few days. Most patients don't require any anti-emetics for this side effect.

Occasionally, there may be myalgia or lethargy lasting for few weeks. The symptoms subside gradually or may require reporting to your doctor.

There is no interaction of Denvax therapy with your alcohol intake.

Uncommon Side Effects – less than 1% patients develop hypotension that requires medical attention. Please report to your doctor if you feel excessive sweating/lethargy or sleepiness.

Most patients adapt to Denvax treatment by the second dose of therapy and less than 0.1% doses in all patients given Denvax therapy have given sustained side effects with second and third dose.

Important information

It is very important that you verify your name, identification code and address, mentioned clearly on the vials supplied to you. ICT, Noida holds no liability for lack of adequate checking on consumer's part.

Storage of vials

Denvax cannot be stored beyond 30 hours of its packaging. It is supplied to you in cold chain carriers where the optimum temperature is between 4°-8°C. The expiry date and time are mentioned on the vials. Denvax can only be taken within 30 hours of packaging. Please ensure all preparations for receiving and administering of the vaccine on the specified date and time.

If you want to delay it for some reasons, the Denvax can remain stored for you for maximum of 30 days in our lab at ICT, Noida. For this you need to inform at least 48 hours before the delivery date. Please note: Once the vaccine is on its way for delivery, it cannot be taken back for storage.

More Information

For more information, please contact us at:

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