ELIAS Cancer Immunotherapy (ECI®) — Autologous Prescription Product

Restricted to use by or under the direction of a veterinarian

INTRODUCTION

This product, the ELIAS Cancer Immunotherapy (ECI®), consists of a series of attenuated autologous cancer cell vaccines and an activated T cell infusate. For the treatment of dogs with osteosarcoma. This product has demonstrated a reasonable expectation of efficacy and a preliminary safety profile for the treatment of dogs with appendicular osteosarcoma without thoracic radiographic evidence of metastasis, in conjunction with amputation. This is an autologous prescription product for the use by, or under the supervision of, a veterinarian; safety, efficacy, and potency have not been fully evaluated. For more information regarding safety, see productdata.aphis.usda.gov.

ECI® is an adoptive cell therapy which conditions a patient's immune cells (T cells) to recognize their own cancer cells and initiate an immune response against them. To manufacture the autologous cancer cell vaccines, patient's cancer cells are surgically removed (e.g., at amputation of the affected limb) via sterile technique. To manufacture the T cell infusate, mononuclear cells (MNCs) are collected from the patient via apheresis after the vaccination series.

STORAGE REQUIREMENTS AND APPEARANCE

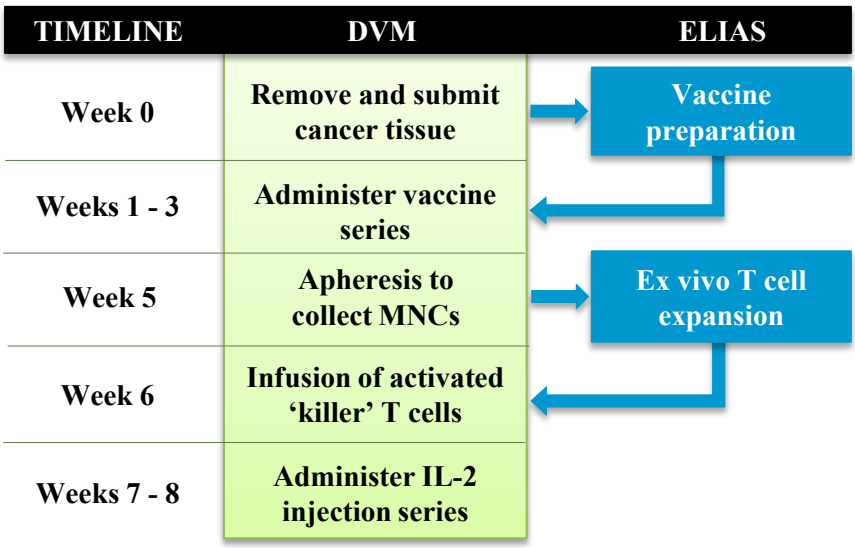
Vaccine: Store at -65 to -85 °C. Supplied in a cryovial containing an opaque to slightly pink or tan solution.

T cell infusate: Store at 2 to 8 °C. Supplied in an infusion bag containing an opaque to slightly pink or tan solution.

DIRECTIONS

The overall duration of the ECI® protocol is approximately 8 weeks (see Figure 1).

FIGURE 1: Schematic Overview of the ECI® Protocol



Vaccines are administered as a series of 3 vaccinations separated by 7 ± 2 days between administrations. Immediately prior to vaccination, thaw 1 vaccine cryovial. Route of administration is via intradermal injection of 0.25 mL into each of 4 administration sites (see Figure 2a).

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DIRECTIONS contd.

Vaccines are given intradermally in 4 sites (see Figure 2a). These sites were chosen to enable the contents of the vaccine to drain into the major chains of lymph nodes and reach maximal numbers of lymph node T cells. If limb is absent, inject proximally and adjacent to the nearest draining lymph node. For proper intradermal technique, place needle at a 10-15° angle to the skin (see Figure 2b). This is a shallow injection that should create a tense wheal, or blister, under the skin. Inject the complete contents of each syringe. Inactivate unused contents before disposal.

FIGURE 2a: Intradermal Vaccine Administration Sites

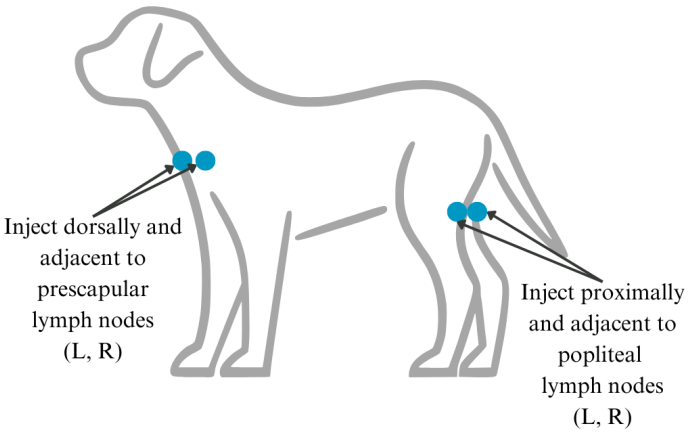
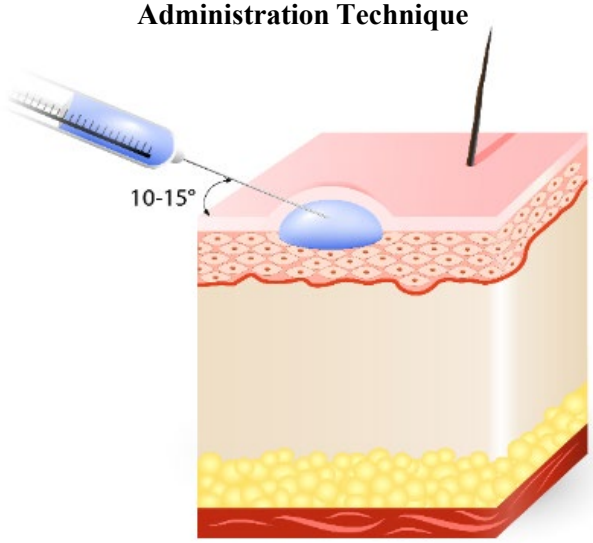


FIGURE 2b: Intradermal Vaccine Administration Technique



T cell infusate is administered as an intravenous infusion at 7 ± 2 days following apheresis. Approximately 1 hour prior to infusion, administer pre-medicants: diphenhydramine at 2 mg/kg given intramuscularly to minimize inflammatory type reactions and maropitant citrate at 1 mg/kg given subcutaneously to prevent vomiting. Route of administration of the T cell infusate is via intravenous infusion over a minimum of 30 minutes using a non-peristaltic pump with a 170-210 micron filter on the infusion line. The infusion bag is washed with a volume of 10-20 mL of sterile saline to ensure that the total dose is infused. IL-2 is administered subcutaneously at a concentration of 20,000 IU/kg starting the day after T cell infusion, then every other day for a total of 5 doses. Inactivate unused contents before disposal.

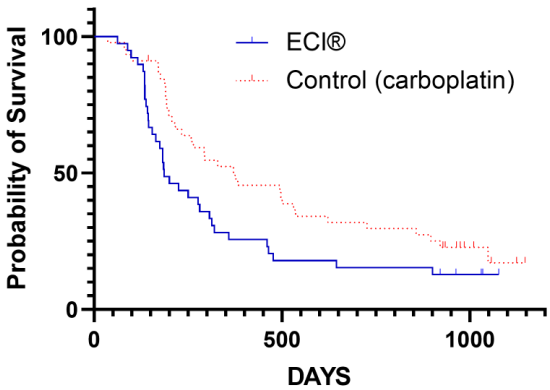
EFFICACY

A reasonable expectation of efficacy was demonstrated in a multi-site, prospective, randomized, positive-controlled, open label clinical trial. Dogs were randomized into one of two treatment cohorts of either ECI® or the positive control (carboplatin). All dogs underwent amputation surgery to remove the primary tumor‡ and then started their designated treatment. A total of 86 dogs were evaluated for efficacy (ECI® = 40; Control = 46).

The Kaplan-Meier plot of the efficacy data is shown in Figure 3.

‡ 3% of cancer tissue specimens processed for dogs randomized in the study did not result in usable vaccines.

FIGURE 3: Kaplan-Meier Survival Plot



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EFFICACY contd.

Table 1 presents the survival data for each cohort at the 12-, 18- and 30-month endpoints.

TABLE 1: 12-, 18-, 30-Month Survival Data

Endpoint/Metric	ECI®	Control (carboplatin)
12-Month Survival	30/40 died	23/46 died
Survival Rate	0.25	0.51
18-Month Survival	33/40 died	31/46 died
Survival Rate	0.17	0.33
30-Month Survival	35/40 died	35/46 died
Survival Rate	0.13	0.25
Median Survival Time	186 days	371 days

SAFETY

A combined pivotal field safety and efficacy study demonstrated that ECI® was well-tolerated. A total of 49 client-owned dogs were evaluated for safety. In the study, autologous vaccines and T cell infusates were administered to 49 and 45 dogs, respectively. All reported adverse reactions (ARs) were mild to moderate in severity (see Table 2). The following text/tables only identify the most common or consequential ARs that were reasonably associated with the use of this product. For more complete information on all adverse events, see productdata.aphis.usda.gov.

TABLE 2: Summary of Adverse Reactions

	Total Dogs Evaluated	Adverse Reaction	Any Grade AR	Serious Adverse Reactions VCOG Grades 3-5
Autologous Vaccine	49	Lethargy/fatigue	8 (16.3%)	0
		Anorexia	6 (12.2%)	0
		Diarrhea	5 (10.2%)	0
		Personality/behavior	5 (10.2%)	0
		Nausea/ptyalism	3 (6.1%)	0
		Vomiting	3 (6.1%)	0
T cell Infusate	45	Lethargy/fatigue	8 (17.8%)	0
		Anorexia	7 (15.6%)	0
		Nausea/ptyalism	6 (13.3%)	0
		Fever	5 (11.1%)	0
		Diarrhea	3 (6.7%)	0

Adverse Reaction represents the most appropriate term from VCOG-CTCAE v1.1 (Veterinary Cooperative Oncology Group, 2011, Veterinary and Comparative Oncology 4:417-446). Only the worst grade of an AR is included in the occurrence calculation. Grade 1 and 2 ARs are considered mild to moderate with no or outpatient intervention required. Grade 3-5 ARs are severe to life-threatening. Grade 5 results in death. ARs that occurred in ≥5% of all doses administered or were Grade 3-5 are included.

Additional adverse reactions reported during other prelicense studies or post licensure product use that were reasonably associated with the use of the T cell infusate included vomiting.

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CONTRAINDICATIONS

Glucocorticoids or any other immunosuppressive drugs are not permitted beginning 14 days prior to surgery until 30 days following end of treatment. Immunomodulating drugs, herbal supplements, and other naturopathic therapies are not permitted beginning at surgery until 30 days following T cell infusion. If necessary, dexamethasone is permitted to mitigate serious adverse events following T cell infusion (see PRECAUTIONS).

PRECAUTIONS

To minimize the occurrence of severe immune related inflammatory effects at time of T cell infusion, pre-medicants should be administered (see DIRECTIONS).

In rare instances, a serious immunologic event known as cytokine release syndrome (CRS) can occur following T cell infusion. CRS is an acute systemic inflammatory syndrome characterized by fever, hypotension, and hypoxia. Patients should be monitored by the veterinarian for 4-6 hours post-infusion for clinical signs of CRS. Follow treatment recommendations in Table 3 for CRS management.

TABLE 3: Cytokine Release Syndrome: Clinical Description of Severity and Recommended Treatment

	Severity			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Clinical Signs	Fever (>39.5°C/103.5°F) with or without constitutional signs	Hospitalization for observation/supportive care without requirement for pressors or oxygen supplementation; hypotension responding to intravenous fluids	Hypotension managed with one pressor; hypoxia requiring non-invasive oxygen support (flow-by/prongs/mask/ oxygen cage)	Life-threatening consequences; urgent intervention required; hypoxia requiring mechanical ventilation
Recommended Treatment	Monitor signs	IV fluids are indicated	Dexamethasone (0.25 mg/kg, IV, once daily, as necessary)	Dexamethasone (0.25 mg/kg, IV, once daily, as necessary)

WARNINGS

Not for use in humans. In case of human exposure, contact a physician.

Do not mix with other products.

This product has not been tested in lactating, breeding or pregnant animals.

Efficacy, safety, and/or potency have not been established for the treatment of other diseases or other species that are not described on this insert.

Patients should be monitored by the veterinarian for 4-6 hours post-infusion for clinical signs of cytokine release syndrome (CRS). If observed, follow treatment recommendations in Table 3 of the Product Insert for CRS management.

To report suspected adverse events or for additional information, contact ELIAS Animal Health at 1-833-941-5858.

ELIAS® ANIMAL HEALTH

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