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**FDA FILES APPLICATION TO CONVERT ONTAK<sup>®</sup> (DENILEUKIN DIFTITOX) TO FULL APPROVAL FOR USE IN CUTANEOUS T-CELL LYMPHOMA (CTCL)**

*sBLA Submission Based on Data from Placebo-Controlled Phase III Trial;  
Largest Enrollment of CTCL Patients in a Randomized Study*

**WOODCLIFF LAKE, N.J., June 26, 2008** – Eisai Corporation of North America announced today that the U.S. Food and Drug Administration (FDA) has accepted for priority review a supplemental biologics license application (sBLA) for ONTAK<sup>®</sup>. The sBLA seeks to convert an accelerated approval indication into full approval. It is based on a placebo-controlled Phase III clinical trial to confirm the clinical effectiveness of ONTAK in certain patients with cutaneous T-cell lymphoma (CTCL).

ONTAK is indicated for the treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor. The safety and efficacy of ONTAK in patients with CTCL whose malignant cells do not express the CD25 component of the IL-2 receptor have not been examined. ONTAK was granted accelerated approval under Subpart E in February 1999.

CTCL is a rare form of cancer in which T-cells, cells that the body uses to fight infections, become cancerous and affect the skin. CTCL can also spread to other organs in a small number of patients.

Subpart E is an FDA regulation that allows the accelerated approval of a biologic agent based on a surrogate endpoint or an effect on a clinical endpoint other than survival and is most common in serious diseases or for medications that fill an unmet medical need. All Subpart E approvals are contingent on the completion of post-marketing clinical trials that confirm a clinical benefit of the biologic agent.

**About ONTAK**

ONTAK is a genetically engineered fusion toxin protein consisting of the amino acid sequences for the enzymatically-active portion of diphtheria toxin fused to the sequence of human interleukin-2, resulting in a molecule that is cytotoxic for cells bearing the target IL-2 receptor.

ONTAK is indicated for the treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor (see PRECAUTIONS, Laboratory Tests, in full prescribing information for CD25 expression testing). The safety and efficacy of ONTAK in patients with CTCL whose malignant cells do not express the CD25 component of the IL-2 receptor have not been examined.

**IMPORTANT SAFETY INFORMATION**

**WARNING: Only physicians experienced in the use of antineoplastic therapy and management of patients with cancer should use ONTAK (denileukin diftitox). Patients treated with denileukin diftitox must be managed in a facility equipped and staffed for cardiopulmonary resuscitation and where the patient can be closely monitored for an appropriate period based on his or her health status.**

**CONTRAINDICATIONS:**

ONTAK is contraindicated for use in patients with a known sensitivity to denileukin diftitox or any of its components: diphtheria toxin, IL-2, or excipients.

**WARNINGS:****Acute Hypersensitivity-type Reactions**

- Acute hypersensitivity reactions were reported in 98 of 143 patients (69%) during or within 24 hours of ONTAK infusion; approximately half of the events occurred on the first day of dosing regardless of the treatment cycle.
- The constellation of symptoms included one or more of the following, defined as the incidence (%) in these 98 patients: hypotension (50%), back pain (30%), dyspnea (28%), vasodilation (28%), rash (25%), chest pain or tightness (24%), tachycardia (12%), dysphagia or laryngismus (5%), syncope (3%), allergic reaction (1%), or anaphylaxis (1%). These events were severe in 2% of patients.
- Death during infusion has been reported.

**Vascular Leak Syndrome**

- This syndrome, characterized by 2 or more of the following 3 symptoms was reported in 27% (38/143) of patients in the clinical studies: hypotension, edema, hypoalbuminemia.
- Six percent (8/143) of patients were hospitalized for the management of these symptoms.
- The onset of symptoms in patients with vascular leak syndrome was delayed, usually occurring within the first two weeks of infusion; symptoms may persist or worsen after the cessation of denileukin diftitox.
- Cases of vascular (capillary) leak with a fatal outcome have been reported.
- Special caution should be taken in patients with preexisting cardiovascular disease (See ADVERSE REACTIONS, Cardiovascular System).

Weight, edema, blood pressure, and serum albumin levels should be carefully monitored on an outpatient basis. This syndrome is usually self-limited and treatment should be used only if clinically indicated. The type of treatment will depend on whether edema or hypotension is the primary clinical problem. Pre-existing low serum albumin levels appear to predict and may predispose patients to the syndrome (see PRECAUTIONS, Laboratory Tests).

**Visual Loss**

Loss of visual acuity, usually with loss of color vision, with or without retinal pigment mottling has been reported following administration of ONTAK. Recovery was reported in some of the affected patients; however, most patients reported persistent visual impairment.

**PRECAUTIONS:****General**

Patients should be monitored carefully for infection since patients with CTCL have a predisposition to cutaneous infection.

**Pregnancy Category C**

Animal reproduction studies have not been conducted with ONTAK. It is also not known whether ONTAK can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. ONTAK should be given to a pregnant woman only if clearly needed.

**Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, patients receiving ONTAK should discontinue nursing.

**ADVERSE REACTIONS:**

Twenty-one percent (30/143) of patients required hospitalization for drug-related adverse events; the most common reasons were evaluation of fever, management of vascular leak syndrome or dehydration secondary to gastrointestinal toxicity.

The most commonly reported adverse reactions associated with the use of ONTAK therapy (n=143 patients) include hypoalbuminemia (83%), chills/fever (81%), asthenia (66%), nausea/vomiting (64%), transaminase increase (61%), infection (48%), pain (48%), edema (47%), hypotension (36%), anorexia (36%), and rash (34%).

**Post-Marketing:**

The following adverse reactions have been identified during post approval use of ONTAK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Special Senses: See WARNINGS: Visual Loss

For detailed safety information and full prescribing information about ONTAK (denileukin diftitox), please visit [www.eisai.com](http://www.eisai.com).

**About CTCL**

Cutaneous T-cell lymphoma (CTCL) is a collective term for a group of rare malignant lymphomas. In patients with CTCL, certain cells that the body uses to fight infections, called T-cells, become cancerous and frequently result in skin lesions. CTCL is a slowly progressive disease for which there is no known cure. According to a recent study, CTCL affects approximately 1,900 people annually in the U.S. (6.4 cases per million people).

**About Eisai Corporation of North America**

Eisai Corporation of North America is a wholly-owned subsidiary of Eisai Co., Ltd., a research-based *human health care (hhc)* company that discovers, develops and markets products throughout the world. Eisai focuses its efforts in three therapeutic areas: neurology, gastrointestinal disorders and oncology/critical care.

Eisai Corporation of North America supports the activities of its operating companies in North America, which include: Eisai Research Institute of Boston, Inc., a discovery operation with strong organic chemistry capabilities; Morphotek, Inc., a biopharmaceutical company specializing in the development of therapeutic monoclonal antibodies; Eisai Medical Research Inc., a clinical development group; Eisai Inc., a commercial operation with manufacturing and marketing/sales functions; and Eisai Machinery U.S.A., which markets and maintains pharmaceutical manufacturing machinery.

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