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FDA Grants Full Approval to ONTAK[®] (denileukin diftitox) For Use in Patients with Cutaneous T-Cell Lymphoma (CTCL)

Conversion from Accelerated Approval Based on Largest Phase III Placebo-Controlled Trial Ever Conducted in CTCL

WOODCLIFF LAKE, N.J., October 15, 2008 – Eisai Corporation of North America announced today that the U.S. Food and Drug Administration (FDA) has approved an efficacy supplemental biologics license application (sBLA) for ONTAK[®] (denileukin diftitox) solution for intravenous injection for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) whose malignant cells express the CD25 component of the interleukin (IL)-2 receptor (CD25+). A separate efficacy supplement that included data from patients with CTCL whose malignant cells did not test positive for the CD25 component of the IL-2 receptor received a complete response letter.

The FDA's action, following a priority review, marks the conversion of an accelerated approval indication to full approval and is based on data from a Phase III clinical trial that evaluated the overall efficacy and safety of ONTAK in certain patients with CTCL. CTCL is a term for a group of rare malignant lymphomas with primary manifestation in the skin. This trial was the largest Phase III, randomized, double-blind, placebo-controlled trial ever conducted in CTCL.

The study met its primary endpoint of overall response rate (ORR). ORR is the sum of complete and partial responses seen in a study, divided by the number of evaluable patients. The ORR was 46% for the 18 mcg/kg/day dose of ONTAK ($p=0.002$ vs. placebo) and 37% for the 9 mcg/kg/day dose ($p=0.03$ vs. placebo) vs. 15% for placebo. In addition, analysis* of a secondary endpoint, progression-free survival (PFS), suggested a 73% reduction in risk of disease progression in the 18 mcg/kg/day group (hazard ratio=0.27, $p=0.0002$, 95% CI 0.14, 0.54) and a 58% reduction in risk of disease progression in the 9 mcg/kg/day group (hazard ratio=0.42, $p=0.02$, 95% CI 0.20, 0.86) compared to placebo.

“These data confirm the benefit of the safety and efficacy profiles of ONTAK. We are also encouraged that the data indicate a significant reduction in risk of disease progression compared to placebo,” said Francine M. Foss, MD, Professor of Medicine, Assistant Director of Clinical Investigation, Hematologic Malignancies at Yale Cancer Center. “Physicians can have confidence in ONTAK since it is the most extensively studied agent in CTCL.”

* Results were determined based on a Cox regression analysis stratified by randomization ratio and adjusted for disease stage.

“The full approval of ONTAK is in keeping with our *human health care* mission, to address the unmet medical needs of patients with CTCL,” said Hajime Shimizu, Chairman and CEO, Eisai Corporation of North America. “As an orphan drug indicated for a rare disease, ONTAK has the potential to make a difference for this patient population.”

Study Details

The Phase III trial was a randomized, double-blind, placebo-controlled, parallel-group study to confirm the effectiveness and safety of ONTAK in CD25+ patients with refractory CTCL (stages Ia-III). The study enrolled a total of 144 patients with CTCL whose malignant cells expressed the CD25 component of the IL-2 receptor. Patients were randomized to receive either of two doses of ONTAK [18 mcg/kg/day (n=55) or 9 mcg/kg/day (n=45)] or placebo (n=44) for up to eight cycles of therapy. Approximately two-thirds (67%) of the patients had stage IIa or lower and one-third (33%) had stage IIb or III. Patients were randomized to receive ONTAK via intravenous infusion on days one to five of each 21-day cycle. The median number of cycles for all ONTAK-treated patients was six for the 18 mcg/kg/day group (range 1-11) and seven for the 9 mcg/kg/day group (range 1-10).

“The efficacy data from this placebo-controlled, randomized trial is important and suggests that dermatologists and oncologists should collaborate to ensure that CTCL patients are treated appropriately at each stage of their disease,” said Madeleine Duvic, MD, Professor of Internal Medicine and Dermatology, Deputy Chairman Department of Dermatology, University of Texas MD Anderson Cancer Center. “Patients with CTCL may also wish to visit a CTCL center of excellence, in which both specialties are represented, to discuss treatment options.”

In the Phase III clinical trial, 25% of ONTAK-treated patients (25/100) experienced a serious adverse event. The most common serious adverse events in ONTAK-treated patients in the study were capillary leak syndrome (4%), dehydration (4%), pyrexia (3%), hypotension (2%), skin disorder (2%), chest pain (2%), hypoalbuminemia (2%) and fatigue (2%). ONTAK was discontinued in 20 patients (20%) due to one or more adverse events.

The most common adverse events, defined as those occurring in greater than or equal to 10% of ONTAK-treated patients and at a higher rate than placebo for the 18 mcg/kg/day, 9 mcg/kg/day dose and placebo groups, respectively, were pyrexia (63.6%; 48.9%; 15.9%), nausea (60%; 46.7%; 22.7%), rigors (47.3%; 42.2%; 20.5%), fatigue (43.6%; 46.7%; 31.8%), vomiting (34.5%; 13.3%; 6.8%), headache (25.5%; 28.9%; 18.2), peripheral edema (25.5%; 20%; 22.7%), diarrhea (21.8%; 22.2%; 9.1%), anorexia (20%; 8.9%; 4.5%), rash (20%; 24.4%; 4.5%), myalgia (20%; 17.8%; 4.5%), cough (18.2%; 20%; 6.8%), pruritus (18.2%; 15.6%; 9.1%), back pain (18.2%; 15.6%; 2.3%), asthenia (18.2%; 17.8%; 4.5%), hypotension (16.4%; 6.7%; 2.3%), upper respiratory tract infection (12.7%; 13.3%; 11.4%), dizziness (12.7%; 11.1%; 11.4%), arthralgia (12.7%; 15.6%; 11.4%), pain (12.7%; 11.1%; 6.8%), chest pain (12.7%; 4.4%; 2.3%), dysgeusia (10.9%; 0%; 2.3%) and dyspnea (10.9%; 13.3%; 4.5%).

“Patients need to take an active role in managing their CTCL, since this disease may progress and treatment options may change as the disease worsens,” said Judy Jones, President and Co-Founder of the Cutaneous Lymphoma Foundation. “Patients with CTCL should discuss their treatment options, including ONTAK, with their dermatologist or oncologist.”

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS INFUSION REACTIONS, CAPILLARY LEAK SYNDROME AND LOSS OF VISUAL ACUITY.

The following adverse reactions have been reported:

- **Serious and fatal infusion reactions. Administer ONTAK in a facility equipped and staffed for cardiopulmonary resuscitation. Immediately stop and permanently discontinue ONTAK for serious infusion reactions [see *Warnings and Precautions* (5.1)].**
- **Capillary leak syndrome resulting in death. Monitor weight, edema, blood pressure and serum albumin levels prior to and during ONTAK treatment [see *Warnings and Precautions* (5.2)].**
- **Loss of visual acuity and color vision [see *Warnings and Precautions* (5.3)].**

Infusion reactions, defined as symptoms occurring within 24 hours of infusion and resolving within 48 hours of the last infusion in that course, were reported in 70.5% of 234 ONTAK-treated patients across 3 clinical studies. Serious infusion reactions were reported in 8.1% of patients. There have been post-marketing reports of infusion reactions resulting in death.

For patients completing at least 4 courses of ONTAK treatment in a placebo-controlled trial, the incidence of infusion reactions was lower in the third and fourth cycles as compared to the first and second cycles of ONTAK.

Capillary leak syndrome was defined as the occurrence of at least 2 of the following 3 symptoms (hypotension, edema, serum albumin < 3.0 g/dL) at any time during ONTAK therapy. These symptoms were not required to occur simultaneously to be characterized as capillary leak syndrome. As defined, capillary leak syndrome was reported in 32.5% (76/234) of ONTAK-treated patients in clinical studies; one-third required hospitalization or medical intervention to prevent hospitalization. There are post-marketing reports of capillary leak syndrome resulting in death. The onset of symptoms in patients with capillary leak syndrome may be delayed, occurring up to 2 weeks following infusion. Symptoms may persist or worsen after the cessation of ONTAK.

Regularly assess patients for weight gain, new onset or worsening edema and hypotension (including orthostatic changes). Monitor serum albumin levels prior to each course of therapy and more often as clinically indicated. Withhold ONTAK for serum albumin levels less than 3 g/dL.

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.

Increase in ALT/AST from baseline occurred in 84% of ONTAK-treated patients. The majority of these elevations occurred during either the first or second cycle, resolved without medical intervention, and did not require discontinuation of ONTAK.

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

It is not known whether ONTAK 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, a decision should be made to discontinue nursing or to discontinue ONTAK.

In clinical studies (n=234), the most common adverse reactions in ONTAK-treated patients (≥ 20) were pyrexia, nausea, fatigue, rigors, vomiting, diarrhea, headache, peripheral edema, cough, dyspnea and pruritus. The most common serious adverse reactions were capillary leak syndrome (11.1%), infusion reactions (8.1%), and visual changes including loss of visual acuity (4%). ONTAK was discontinued in 28.2% (66/234) of patients due to adverse reactions.

For full prescribing information, including boxed warning, visit www.eisai.com/section.asp?ID=257.

About CTCL

In patients with CTCL, some T-cells, which the body uses to fight infections, become cancerous and result in skin lesions. CTCL is a slowly progressive disease for which there is no known cure. Approximately 2,900 people are diagnosed annually with CTCL in the United States (9.6 cases per million people). The staging of CTCL is based on an evaluation of the type and extent of skin lesions and the extent of lymph node, peripheral blood and visceral involvement. Stage Ia is the earliest stage and stage IVb is the most advanced.

About ONTAK

ONTAK is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. ONTAK is a genetically-engineered cytotoxic fusion 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 was granted approval in February 1999 under Subpart E, 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. The process by which ONTAK received accelerated approval requires a confirmatory, placebo-controlled Phase III trial. Accelerated approval is most commonly granted in serious diseases or for medications that fill an unmet medical need.

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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