



27 June 2011

Subject: Supply Interruption of ONTAK<sup>®</sup> (denileukin diftitox) Drug Product

Sometime during the week of June 27, 2011, a supply interruption of ONTAK Drug Product will occur. Eisai has encountered challenges in the production of ONTAK and is actively working to resolve the manufacturing issue. A trend in certain product characteristics, including out-of-specification results, requires an in-depth process review prior to releasing any further lots. The timing of this process review and any resulting production or testing modifications will result in a supply interruption. We cannot estimate the length of the supply interruption at this time. Updates regarding product availability will be posted on <http://www.ONTAK.com>.

If any of your patients are currently being treated with ONTAK, please communicate with them about the anticipated supply interruption. Eisai has developed an Access Program (Compassionate use program) for patients who are currently receiving ONTAK. Please call Eisai Medical Services at 1-888-422-4743 for specific details on the program including the protocol and informed consent. Please discuss this program as an option for your patients currently receiving ONTAK, along with the potential risks and benefits of participating in the program. Only patients currently receiving ONTAK may participate in the program, and physicians may enroll patients in the Access Program only after appropriate Institutional Review Board review of the Access Program protocol and informed consent.

For more information please contact Eisai Medical Services for any questions about our products at 1-888-422-4743. You may also check ONTAK.com for updates on availability.

Eisai continues to strive towards its goals of meeting the medical needs of patients and their families.

Thank you for your patience and understanding.

## Indication

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.

## Important Safety Information

**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.**
- **Capillary leak syndrome resulting in death. Monitor weight, edema, blood pressure and serum albumin levels prior to and during ONTAK treatment.**
- **Loss of visual acuity and color vision.**

### Infusion Reactions

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

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 postmarketing 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.

### 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.

### **Hepatobiliary Disorders**

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.

### **Pregnancy and Lactation**

ONTAK should be given to a pregnant woman only if clearly needed and should not be used in women who are nursing.

### **Most Common Adverse Reactions**

In clinical studies (n=234), the most common adverse reactions in ONTAK-treated patients ( $\geq 20\%$ ) 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.

Please [click here](#) for the full Prescribing Information.

ONTAK<sup>®</sup> is a registered trademark of Eisai Inc.