

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Ontak safely and effectively. See full prescribing information for Ontak.

ONTAK® (denileukin diftitox) injection, for intravenous use
Initial U.S. Approval: 1999

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

See full prescribing information for complete boxed warning.

- **Serious and fatal infusion reactions. Administer Ontak in a facility equipped and staffed for cardiopulmonary resuscitation. (5.1)**
- **Capillary leak syndrome resulting in death. (5.2)**
- **Loss of visual acuity and color vision. (5.3)**

INDICATIONS AND USAGE

Ontak is a CD25-directed cytotoxin indicated for the treatment of adult patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. (1)

DOSAGE AND ADMINISTRATION

- Premedicate with an antihistamine and acetaminophen prior to each Ontak infusion.
- Administer at 9 or 18 mcg/kg/day by intravenous infusion over 30 to 60 minutes for 5 consecutive days every 21 days for 8 cycles. (2.1, 2.2)

DOSAGE FORMS AND STRENGTHS

Solution in a single-dose vial containing 150 mcg/mL (300 mcg in 2 mL). (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Infusion reactions:** Immediately stop and permanently discontinue Ontak for serious infusion reactions. Monitor patients following infusion. (5.1)
- **Capillary leak syndrome:** Monitor weight, edema, blood pressure and serum albumin levels. Obtain serum albumin levels prior to each course. Delay Ontak until serum albumin is ≥ 3 g/dL. (5.2)
- **Loss of Visual Acuity and Color Vision:** Monitor visual acuity and color vision. (5.3)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 20\%$) were pyrexia, nausea, fatigue, rigors, vomiting, diarrhea, headache, peripheral edema, cough, dyspnea and pruritus. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-877-873-4724 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Schedule and Administration
- 2.2 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Infusion Reactions
- 5.2 Capillary Leak Syndrome
- 5.3 Visual Loss

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Study 1: Placebo Controlled Study in CTCL (Stage Ia to III) Patients
- 14.2 Study 2: Dose Evaluation Study in CTCL (Stage IIb to IVa) Patients

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

- **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)].**

1 INDICATIONS AND USAGE

Ontak[®] is indicated for the treatment of adult patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Schedule and Administration

- Premedicate with an antihistamine and acetaminophen prior to each Ontak infusion.
- Administer at 9 or 18 mcg/kg/day by intravenous infusion over 30-60 minutes for 5 consecutive days every 21 days for 8 cycles.
- Do not administer as a bolus injection.
- Withhold administration of Ontak if serum albumin levels are less than 3 g/dL.
- Discontinue for Grade 3 or higher adverse infusion reactions.

2.2 Preparation and Administration

- Thaw vials in the refrigerator at 2 to 8°C (36 to 46°F) for not more than 24 hours or at room temperature for 1 to 2 hours.
- Bring Ontak to room temperature, before preparing the dose.
- Mix the solution in the vial by gentle swirling; do not shake.
- Visually inspect for particulate matter and discoloration prior to administration, whenever solution and container permit. Use only if the solution is clear, colorless and without visible particulate matter. After thawing, a haze may be visible which should clear when the solution is at room temperature.
- Do not refreeze Ontak after thawing.
- Prepare and hold diluted Ontak in plastic syringes or soft plastic intravenous bags. Do not use glass containers.
- Maintain concentration of Ontak at 15 mcg/mL or higher during all steps in the preparation of the solution for intravenous infusion.

- Withdraw the calculated dose from the vial(s) and inject it into an empty intravenous infusion bag. Do not add more than 9 mL of sterile saline without preservative to the intravenous bag for each 1 mL of Ontak.
- Do not mix Ontak with other drugs.
- Do not administer Ontak through an in-line filter.
- Administer prepared solutions of Ontak within 6 hours, using a syringe pump or intravenous infusion bag.
- Discard unused portions of Ontak immediately.

3 DOSAGE FORMS AND STRENGTHS

Injection: 150 mcg/mL (300 mcg in 2 mL) in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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% (165/234) of Ontak-treated patients across 3 clinical studies utilizing the approved doses and schedule. Serious infusion reactions were reported in 8.1% (19/234) of Ontak-treated patients. There have been post-marketing reports of infusion reactions resulting in death.

For patients completing at least 4 courses of Ontak treatment in Study 1 [*see Clinical Studies (14.1)*], the incidence of infusion reactions was lower in the 3rd and 4th cycles as compared to the 1st and 2nd cycles of Ontak.

Resuscitative equipment should be available during Ontak administration. Immediately stop and permanently discontinue Ontak for Grade 3 or higher infusion reactions.

5.2 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 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. Among these 76 patients with capillary leak syndrome, one-third required hospitalization or medical intervention to prevent hospitalization. There have been 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, hypotension (including orthostatic changes) and monitor serum albumin levels prior to the initiation of each course of therapy and more often as clinically indicated. Withhold Ontak for serum albumin levels of less than 3 g/dL.

5.3 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.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the label:

- Infusion Reactions [see Warnings and Precautions (5.1)]
- Capillary Leak Syndrome [see Warnings and Precautions (5.2)]
- Visual Loss [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data are available for 3 clinical studies in which 234 patients received Ontak at 9 mcg/kg (n=80) or 18 mcg/kg (n=154) at the recommended schedule. Of these studies, 1 was placebo-controlled and dose-ranging (Study 1, 100 Ontak-treated patients), one was a dose-comparison of 9 and 18 mcg/kg (Study 2, n=71), and the third was a single-arm study using 18 mcg/kg (n=63); all studies were limited to adult patients with CTCL. The median age of patients across the clinical studies was 60 years (range 23-91 years) and 36% (n=85) were 65 years of age or older; 55% were men and 85% were Caucasian.

Across all 3 studies, 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.

The data described in Table 1 reflect exposure to Ontak in 100 patients administered as a single agent at the recommended dosing schedule in the randomized placebo-controlled trial (Study 1). The median number of Ontak cycles was 7 (range 1-10) for the 9 mcg/kg cohort and 6 (range 1-11) for the 18 mcg/kg cohort. The median age of patients was 59 years (range 23-84 years) and 34% (n=34) were 65 years of age or older; 55% were men and 86% were Caucasian.

Adverse Reaction	Placebo N=44 n (%)	Ontak 9 mcg/kg N=45 n (%)	Ontak 18 mcg/kg N=55 n (%)
Pyrexia	7 (15.9)	22 (48.9)	35 (63.6)

Nausea	10 (22.7)	21 (46.7)	33 (60.0)
Rigors	9 (20.5)	19 (42.2)	26 (47.3)
Fatigue	14 (31.8)	21 (46.7)	24 (43.6)
Vomiting	3 (6.8)	6 (13.3)	19 (34.5)
Headache	8 (18.2)	13 (28.9)	14 (25.5)
Edema peripheral	10 (22.7)	9 (20.0)	14 (25.5)
Diarrhea	4 (9.1)	10 (22.2)	12 (21.8)
Anorexia	2 (4.5)	4 (8.9)	11 (20.0)
Rash	2 (4.5)	11 (24.4)	11 (20.0)
Myalgia	2 (4.5)	8 (17.8)	11 (20.0)
Cough	3 (6.8)	9 (20.0)	10 (18.2)
Pruritus	4 (9.1)	7 (15.6)	10 (18.2)
Back pain	1 (2.3)	7 (15.6)	10 (18.2)
Asthenia	2 (4.5)	8 (17.8)	10 (18.2)
Hypotension	1 (2.3)	3 (6.7)	9 (16.4)
Upper respiratory tract infection	5 (11.4)	6 (13.3)	7 (12.7)
Dizziness	5 (11.4)	5 (11.1)	7 (12.7)
Arthralgia	5 (11.4)	7 (15.6)	7 (12.7)
Pain	3 (6.8)	5 (11.1)	7 (12.7)
Chest pain	1 (2.3)	2 (4.4)	7 (12.7)
Dysgeusia	1 (2.3)	0 (0)	6 (10.9)
Dyspnea	2 (4.5)	6 (13.3)	6 (10.9)

Hepatobiliary Disorders: Increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) from baseline occurred in 84% of subjects treated with Ontak (197/234). In the majority of subjects, these enzyme elevations occurred during either the first or the second cycle; enzyme elevation resolved without medical intervention and did not require discontinuation of Ontak.

6.2 Immunogenicity

An immune response to denileukin diftitox was assessed using 2 enzyme-linked immunoassays (ELISA). The first assay measured reactivity directed against intact denileukin diftitox calibrated against anti-diphtheria toxin, and the second assay measured reactivity against the IL-2 portion of the protein. An additional *in vitro* cell-based assay that measured the ability of antibodies in serum to protect a human IL-2R-expressing cell line from toxicity by denileukin diftitox, was used to detect the presence of neutralizing antibodies which inhibited functional activity. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to the intact

fusion protein denileukin diftitox. These results are highly dependent on the sensitivity and the specificity of the assays. Additionally, the observed incidence of the antibody positivity may be influenced by several factors, including sample handling, concomitant medication, and underlying disease. For these reasons, the comparison of the incidence of antibodies to denileukin diftitox with the incidence of antibodies to other products may be misleading.

In Study 1 [see *Clinical Studies (14.1)*], of 95 patients treated with denileukin diftitox, 66% tested positive for antibodies at baseline probably due to a prior exposure to diphtheria toxin or its vaccine. After 1, 2, and 3 courses of treatment, 94%, 99%, and 100% of patients tested positive, respectively. Mean titers of antidenileukin diftitox antibodies were similarly increased in the 9 and 18 mcg/kg/day dose groups after 2 courses of treatment. Meanwhile, pharmacokinetic parameters decreased substantially (C_{max} ~57%, AUC~80%), and clearance increased 2- to 8- fold.

In Study 2 [see *Clinical Studies (14.2)*], 131 patients were assessed for binding antibodies. Of these, 51 patients (39%) had antibodies at baseline. Seventy-six percent of patients tested positive after 1 course of treatment and 97% after 3 courses of treatment. Neutralizing antibodies were assessed in 60 patients; 45%, 73%, and 97% had evidence of inhibited functional activity in the cellular assay at baseline and after 1 and 3 courses of treatment, respectively.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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.

Thyroid conditions: hyperthyroidism, thyroiditis, thyrotoxicosis, and hypothyroidism.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, denileukin diftitox may cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. Advise pregnant women of the potential risk to a fetus. There are no available data on Ontak use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. No animal reproductive and developmental toxicity studies have been conducted with denileukin diftitox .

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population are unknown.

8.2 Lactation

Risk Summary

There are no data on the presence of denileukin diftitox in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with denileukin diftitox and for 7 days after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating Ontak [see *Use in Specific Populations (8.1)*].

Contraception

Females

Ontak may cause embryo-fetal harm when administered to pregnant women [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with Ontak and for at least 7 days after the final dose.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Ontak did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

Doses of approximately twice the recommended dose (31 mcg/kg/day) resulted in moderate-to-severe nausea, vomiting, fever, chills and/or persistent asthenia.

11 DESCRIPTION

Ontak (denileukin diftitox), is a recombinant DNA-derived cytotoxic protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met₁-Thr₃₈₇)-His and the sequences for human interleukin-2 (IL-2; Ala₁-Thr₁₃₃). It is produced in an *E. coli* expression system and has a molecular weight of 58 kD. Neomycin is used in the fermentation process but is undetectable in the final product. Ontak is supplied in single use vials as a sterile, frozen solution intended for intravenous (IV) administration. Each 2 mL vial of Ontak contains 300 mcg of recombinant denileukin diftitox in a sterile solution of citric acid (20 mM), EDTA (0.05 mM) and polysorbate 20 (<1%) in Water for Injection, USP. The solution has a pH range of 6.9 to 7.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Denileukin diftitox is a fusion protein designed to direct the cytotoxic action of diphtheria toxin to cells which express the IL-2 receptor. *Ex vivo* studies report that after binding to the IL-2 receptor on the cell surface, denileukin diftitox is internalized by receptor-mediated endocytosis. The fusion protein is subsequently cleaved, releasing diphtheria toxin enzymatic and translocation domains from the IL-2 fragment, resulting in the inhibition of protein synthesis and ultimately, cell death.

12.3 Pharmacokinetics

Pharmacokinetic parameters associated with denileukin diftitox were determined over a range of doses (3 to 31 mcg/kg/day) in patients with lymphoma. Denileukin diftitox was administered as an intravenous infusion following the schedule used in the clinical trials.

Following the first dose, denileukin diftitox displayed 2-compartment behavior with a distribution phase (half-life approximately 2 to 5 minutes) and a terminal phase (half-life approximately 70 to 80 minutes). Systemic exposure was variable but proportional to dose. Mean clearance was approximately 0.6 to 2.0 mL/min/kg and the mean volume of distribution was similar to that of circulating blood (0.06 to 0.09 L/kg). The mean clearance increased approximately 2- to 8-fold from course 1 to course 3 corresponding to a decrease in exposure of approximately 75%. No accumulation was evident between the first and fifth doses. Gender and age have no effect on pharmacokinetics of denileukin diftitox.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There have been no studies to assess the carcinogenic potential of denileukin diftitox. Denileukin diftitox showed no evidence of mutagenicity in the Ames test and the chromosomal aberration assay. There have been no studies to assess the effect of denileukin diftitox on fertility.

14 CLINICAL STUDIES

14.1 Study 1: Placebo Controlled Study in CTCL (Stage Ia to III) Patients

The safety and efficacy of Ontak were evaluated in a randomized, double-blind, placebo-controlled, 3-arm trial in patients with Stage Ia to III CD25(+) CTCL. Eligible patients were required to have expression of CD25 on $\geq 20\%$ of biopsied malignant cells by immunohistochemistry. Patients were randomized to receive 0, 9 or 18 mcg/kg/day Ontak via intravenous infusion days 1-5 of each 21-day cycle, for up to 8 cycles. Randomization was stratified by disease stage (\leq Ia vs. \geq Iib). The main efficacy outcome was objective response rate (ORR), using a Weighted Skin Severity Index, in conjunction with assessment of lymph node involvement and percentage of abnormal blood lymphocytes. A total of 144 patients were randomized: 44 patients to placebo, 45 patients to 9 mcg/kg/day Ontak and 55 patients to 18 mcg/kg/day Ontak. Randomization for the study was carried out at 1:1:1 for the first 73 patients, 4:1:4 for the next 31 patients, and 1:4:4 for the remaining 40 patients. The median age of patients was 59 years (range 23 to 84 years); 34% were ≥ 65 years. Fifty-five percent were men and 86% were Caucasian. Sixty-seven percent had early stage disease (\leq Ia). Patients had received a median of 2 anti-CTCL therapies (range 0 to 6) prior to study entry. Results for objective response rate (ORR) and progression-free survival (PFS) are shown in the table below.

Efficacy Endpoint	Ontak 18 mcg/kg/day (N=55)	Ontak 9 mcg/kg/day (N=45)	Placebo (N=44)
ORR % ^a	46%	37%	15%
p-value ^b	p=0.002	p=0.03	--
Median Response Duration	220 days	277 days	81 days

PFS ^c	0.27	0.42	
Hazard ratio (95% CI)	(0.14, 0.54)	(0.20, 0.86)	--
p-value	p=0.0002	p=0.02	

a. Adjusted for disease stage and changes in randomization ratios

b. Logistic regression model adjusting for disease stage and changes in randomization ratios over the course of the study; comparisons relative to placebo.

c. Cox regression analysis stratified by randomization ratio and adjusted for disease stage; comparisons relative to placebo.

14.2 Study 2: Dose Evaluation Study in CTCL (Stage IIb to IVa) Patients

A randomized, double-blind study was conducted to evaluate doses of 9 or 18 mcg/kg/day in 71 patients with recurrent or persistent, Stage Ib to IVa CTCL. Entry to this study required demonstration of CD25 expression on at least 20% of the cells in any relevant tumor tissue sample (skin biopsy) or circulating cells. Tumor biopsies were not evaluated for expression of other IL-2 receptor subunit components (CD122/CD132). Ontak was administered as an intravenous infusion daily for 5 days every 3 weeks. Patients received a median of 6 courses of Ontak therapy (range 1 to 11). The study population had received a median of 5 prior therapies (range 1 to 12) with 63% of patients entering the trial with Stage IIb or more advanced stage disease. The median age of patients was 64 years (range 26 to 91 years); 49% were \geq 65 years. Fifty-two percent were men and 75% were Caucasian.

Overall, 30% (95% CI: 18-41%) of patients treated with Ontak experienced an objective tumor response (50% reduction in tumor burden which was sustained for \geq 6 weeks; Table 3). Seven patients (10%) achieved a complete response and 14 patients (20%) achieved a partial response. The overall median duration of response, measured from first day of response, was 4 months with a median duration for complete response of 9 months and for partial response of 4 months.

Clinical Response	9 mcg/kg/day	18 mcg/kg/day
Complete Response	9% (3/35)	11% (4/36)
95% Confidence Interval	(2%, 23%)	(3%, 26%)
Partial Response	14% (5/35)	25% (9/36)
95% Confidence Interval	(9%, 30%)	(12%, 42%)
Overall Response	23% (8/35)	36% (13/36)
95% Confidence Interval	(10%, 40%)	(21%, 54%)

16 HOW SUPPLIED/STORAGE AND HANDLING

Ontak is supplied as 150 mcg/ml, sterile, frozen solution (300 mcg in 2 mL) in a sterile single-dose vial.

NDC 62856-603-01, 6 vials in a package.

Store frozen at or below -10°C (14°F).

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to and during treatment with Ontak.

Infusion Reactions

Inform patients of the signs and symptoms of infusion reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions [*see Warnings and Precautions (5.1)*].

Capillary Leak Syndrome

Inform patients of the signs and symptoms of capillary leak syndrome. Advise patients to contact their healthcare provider immediately for signs and symptoms of capillary leak syndrome [*see Warnings and Precautions (5.2)*].

Visual Loss

Advise patients to inform their healthcare provider if they experience visual changes [*see Warnings and Precautions (5.3)*].

Pregnancy

Inform pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Females and Males of Reproductive Potential

Advise female patients of reproductive potential to use effective contraception during treatment with Ontak and for 7 days after the final dose [*see Use in Specific Populations (8.3)*].

Lactation

Advise women not to breastfeed during treatment with Ontak and for 7 days after the final dose [*see Use in Specific Populations (8.2)*].

Manufactured and Distributed by:

Eisai Inc.

Woodcliff Lake, NJ 07677

US License No. 1862