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3000301 (Rev. 0299)

ONTAK® (denileukin diftitox)

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.

DESCRIPTION

ONTAK® (denileukin diftitox), a recombinant DNA-derived cytotoxic protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met₁-Thr₃₈₇-His) followed by the sequences for interleukin-2 (IL-2; Ala₁-Thr₁₃₃), is produced in an *E. coli* expression system. ONTAK has a molecular weight of 58 kD. Neomycin is used in the fermentation process but is undetectable in the final product. The product is purified using reverse phase chromatography followed by a multistep diafiltration process.

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 of 6.9 to 7.2.

CLINICAL PHARMACOLOGY

General: Denileukin diftitox is a fusion protein designed to direct the cytotoxic action of diphtheria toxin to cells which express the IL-2 receptor. The human IL-2 receptor exists in three forms, low (CD25), intermediate (CD122/CD132) and high (CD25/CD122/CD132) affinity. The high affinity form of this receptor is usually found only on activated T lymphocytes, activated B lymphocytes and activated macrophages. Malignant cells expressing one or more of the subunits of the IL-2 receptor are found in certain leukemias and lymphomas including cutaneous T-cell lymphoma (CTCL). *Ex vivo* studies suggest that denileukin diftitox interacts with the high affinity IL-2 receptor on the cell surface and inhibits cellular protein synthesis, resulting in cell death within hours.

The biodistribution and excretion of radiolabeled denileukin diftitox were evaluated over 48 hours in rats. The liver and kidneys were the primary sites of distribution and accumulation of radiolabeled material outside of the vasculature. Denileukin diftitox was metabolized by proteolytic degradation. Excreted material was less than 25% of the total injected dose and consisted of low molecular weight breakdown products.

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 IV 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. Clearance was approximately 1.5 to 2.0 mL/min/kg and the volume of distribution was similar to that of circulating blood (0.06 to 0.08 L/kg). No accumulation was evident

in patients with lymphoma whose malignant cells express the CD25 component of the IL-2 receptor (See **PRECAUTIONS**, Laboratory Tests, for CD25 expression testing). The safety and efficacy of denileukin diftitox in patients with CTCL whose malignant cells do not express the CD25 component of the IL-2 receptor have not been examined.

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CLINICAL STUDIES

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 IV 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 Ib or more advanced stage disease. 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 ≥ 6 weeks; Table 1). 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. In a Phase III dose-escalation study, 35 patients with Stage Ia to IVb CTCL were treated. ONTAK was administered as an IV infusion at doses ranging from 3 to 31 mcg/kg/day, daily for 5 days every 3 weeks. The overall response rate in patients with CTCL who expressed CD25 was 38% (12 of 32 patients); the complete response rate was 16% and the partial response rate was 22%. There were no responses in 21 patients with Hodgkin's Disease.

Table 1
Response in the Phase III Double-Blind Study
Patients with CTCL

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

Immunogenicity: Prior to therapy, 39% (51/131) of lymphoma patients had low titers (<1:5) of antibody which cross-reacted with the diphtheria toxin domains of denileukin diftitox, presumably due to prior diphtheria immunization. Development of anti-denileukin diftitox antibodies was observed in 41/49 patients after a single course and in 33/34 patients after 3 cycles. Following anti-denileukin diftitox antibody formation, there was a significant increase (two to threefold) in clearance, which resulted in a decrease in mean systemic exposure of approximately 75%. Changes in clearance were related to the development of antibodies.

The antibody response in all such patients was directed against the diphtheria toxin domain. A low titer of antibodies to the IL-2 portion of the denileukin diftitox molecule also developed in approximately 50% of patients. The presence or absence of antibodies did not correlate with the risk of immediate hypersensitivity-type infusional adverse events.

INDICATIONS

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 (See **PRECAUTIONS**, Laboratory Tests, for

CD25 expression testing). The safety and efficacy of denileukin diftitox in patients with CTCL whose malignant cells do not express the CD25 component of the IL-2 receptor have not been examined.

CONTRAINDICATIONS

ONTAK is contraindicated for use in patients with a known hypersensitivity to denileukin diftitox or any of its components: diphtheria toxin, interleukin-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. Management consists of interruption or a decrease in the rate of infusion (depending on the severity of the reaction); 3% of infusions were terminated prematurely and reduction in rate occurred in 4% of the infusions during the clinical trials. The administration of IV antihistamines, corticosteroids, and epinephrine may also be required; two subjects received epinephrine and 18 (13%) received systemic corticosteroids in the clinical studies. These drugs and resuscitative equipment should be readily available during ONTAK administration.

Vascular Leak Syndrome: This syndrome, characterized by 2 or more of the following 3 symptoms (hypotension, edema, hypoalbuminemia) was reported in 27% (38/143) of patients in the clinical studies. 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 and may persist or worsen after the cessation of denileukin diftitox. 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).

PRECAUTIONS

General: Patients should be monitored carefully for infection since patients with CTCL have a predisposition to cutaneous infection. Also, the binding of denileukin diftitox to activated lymphocytes and macrophages can lead to cell death and may impair immune function in patients.

Laboratory Tests: Prior to administration of this product, the patient's malignant cells should be tested for CD25 expression. A testing service for the assay of CD25 on skin biopsy samples is available. For information on this service call 800-964-5836.

A complete blood count and a blood chemistry panel, including liver and renal function and serum albumin levels, should be performed prior to initiation of ONTAK treatment and weekly during therapy.

Eighty-three percent (118/143) of patients with lymphoma experienced hypoalbuminemia, which was considered moderate or severe in 17% (20/118) of the affected patients. For most patients, the nadir for hypoalbuminemia occurs one to two weeks after ONTAK administration. Serum albumin levels should be monitored prior to the initiation of each treatment course. Administration of ONTAK should be delayed until serum albumin levels are at least 3.0 g/dL (see **WARNINGS**).

Drug Interactions: No clinical drug interaction studies have been conducted. However, in a single *in vivo* rodent study denileukin diftitox had no effect on P450 levels.

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.

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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.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Forty-nine percent (35/71) of the patients enrolled in the randomized two dose study were 65 years of age or older, and those patients had response rates similar to those seen in younger patients. The following adverse events (regardless of causality) tended to be more frequent and/or more severe in lymphoma patients who were 65 years of age or older: anorexia, hypotension, anemia, confusion, rash, nausea and/or vomiting.

ADVERSE REACTIONS

Adverse reactions are presented in Table 2. These data are based on adverse reactions observed in two clinical studies of 143 patients with lymphoma, including 105 patients with CTCL, treated at doses ranging from 3 to 31 mcg/kg/day.

All patients experienced one or more adverse events. Twenty-one percent 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. Five percent of clinical adverse reactions were severe or life-threatening. The occurrence of adverse events tended to diminish in frequency after the first two courses, possibly related to antibody development.

Table 2
Adverse Reactions Occurring in
Lymphoma Patients
(Frequency ≥ 5% of Patients)
N = 143 patients

Body System	Combined Term	All Grades n (%)	Grades 3 and 4 n (%)
Body as a Whole			
	Chills/fever	116 (81)	31 (22)
	Asthenia	95 (66)	31 (22)
	Infection	69 (48)	34 (24)
	Pain	69 (48)	19 (13)
	Headache	37 (26)	5 (3)
	Chest pain	34 (24)	8 (6)
	Flu-like syndrome	11 (8)	0
	Injection site reaction	11 (8)	1 (1)
Cardiovascular			
	Hypotension	52 (36)	11 (8)
	Vasodilation	31 (22)	1 (1)
	Tachycardia	17 (12)	2 (1)
	Thrombotic events	10 (7)	6 (4)
	Hypertension	9 (6)	0
	Arrhythmia	8 (6)	5 (3)
Digestive			
	Nausea/vomiting	91 (64)	20 (14)
	Anorexia	51 (36)	12 (8)
	Diarrhea	42 (29)	5 (3)
	Constipation	13 (9)	2 (1)
	Dyspepsia	10 (7)	0
	Dysphagia	9 (6)	2 (1)
Hematologic and Lymphatic			
	Anemia	26 (18)	9 (6)
	Thrombocytopenia	12 (8)	3 (2)
	Leukopenia	9 (6)	4 (3)
Metabolic and Nutritional			
	Hypoalbuminemia	116 (83)	20 (14)
	Transaminase increase	87 (61)	22 (15)
	Edema	67 (47)	22 (15)
	Hypocalcemia	24 (17)	4 (3)
	Weight decrease	20 (14)	6 (4)
	Dehydration	13 (9)	10 (7)
	Hypokalemia	9 (6)	0
Musculoskeletal			
	Myalgia	25 (17)	3 (2)
	Arthralgia	11 (8)	2 (1)
Nervous			
	Dizziness	31 (22)	1 (1)
	Paresthesia	19 (13)	2 (1)
	Nervousness	16 (11)	2 (1)
	Confusion	11 (8)	8 (6)
	Insomnia	13 (9)	4 (3)
Respiratory			
	Dyspnea	42 (29)	20 (14)
	Cough increase	37 (26)	3 (2)
	Pharyngitis	25 (17)	0
	Rhinitis	19 (13)	2 (1)
	Lung disorder	11 (8)	0
Skin and Appendages			
	Rash	48 (34)	18 (13)
	Pruritus	29 (20)	5 (3)
	Sweating	15 (10)	1 (1)
Urogenital			
	Hematuria	15 (10)	5 (3)
	Albuminuria	14 (10)	1 (1)
	Pyuria	14 (10)	1 (1)
	Creatinine increase	10 (7)	1 (1)

Hypersensitivity: (see WARNINGS)

Vascular Leak Syndrome: (see WARNINGS)

Hypoalbuminemia: (see PRECAUTIONS, Laboratory tests)

Infectious Complications: Infections of various types were reported by 48% (69/143) of the study population, of which 23% (16/69) were considered severe. Six of the 143 patients (4%) discontinued ONTAK therapy because of infections.

Decreased lymphocyte counts (<900 cells/ μ L) occurred in 34% of lymphoma patients. In general, lymphocyte counts dropped during the dosing period (Days 1 to 5) and then returned to normal by Day 15. Smaller changes and more rapid recoveries were observed with subsequent courses.

Infusion-associated Reactions: (see WARNINGS) There are two distinct clinical syndromes associated with ONTAK infusion, an acute hypersensitivity-type symptom complex and a flu-like symptom complex. Overall, 69% of patients had infusion-related, hypersensitivity-type symptoms; for additional information, see WARNINGS. A flu-like syndrome was experienced by 91% of patients within several hours to days after ONTAK infusion. The symptom complex consists of one or more of the following: fever and/or chills (81%), asthenia (66%), digestive (64%), myalgias (18%) and arthralgias (8%). In the majority of patients, these symptoms were mild to moderate and responded to treatment with antipyretics and/or anti-emetics. Antipyretics and/or anti-emetics were used to relieve flu-like symptoms; however, the usefulness of these agents in ameliorating these toxicities or as prophylactic agents to decrease the incidence of the acute, flu-like toxicities has not been prospectively studied.

Gastrointestinal: The onset of diarrhea may be delayed and the duration can be prolonged. Dehydration, usually concurrent with vomiting or anorexia, occurred in 9% of the patients. The majority of transient hepatic transaminase elevations occurred during the first course of ONTAK, were self-limited and resolved within two weeks.

Rash: A variety of rashes were reported, including generalized maculopapular, petechial, vesicular bullous, urticarial and/or eczematous with both acute and delayed onset. Antihistamines may be effective in relieving the symptoms, but more severe rashes may require the use of topical and/or oral corticosteroids.

Cardiovascular System: Two patients, both of whom had known or suspected pre-existing coronary artery disease, sustained acute myocardial infarctions while on study. Ten additional patients (7%) experienced thrombotic events. Two patients with progressive disease and multiple medical problems experienced deep vein thrombosis. Another patient sustained a deep vein thrombosis and pulmonary embolus during hospitalization for management of congestive heart failure and vascular leak syndrome. One patient with a history of severe peripheral vascular disease sustained an arterial thrombosis. Six patients experienced less severe superficial thrombophlebitis. Thrombotic events were also observed in preclinical animal studies.

Infrequent Serious Adverse Events: The following serious adverse events occurred at an incidence of less than 5%: pancreatitis, acute renal insufficiency, microscopic hematuria, hyperthyroidism and hypothyroidism.

OVERDOSAGE

There is no clinical experience with accidental ONTAK overdosage and no known antidote. At a dose of 31 mcg/kg/day, the dose-limiting toxicities were moderate-to-severe nausea, vomiting, fever, chills and/or persistent asthenia. Doses greater than 31 mcg/kg/day have not been evaluated in humans. If overdose occurs, hepatic and renal function and overall fluid balance should be closely monitored.

DOSAGE AND ADMINISTRATION

ONTAK is for intravenous (IV) use only. The recommended treatment regimen (one treatment cycle) is 9 or 18 mcg/kg/day administered intravenously for five consecutive days every 21 days. ONTAK should be infused over at least 15 minutes. If infusion adverse reactions occur (see ADVERSE REACTIONS), the infusion should be discontinued or the rate should be reduced depending on the severity of the reaction. There is no clinical experience with prolonged infusion times (> 80 minutes).

The optimal duration of therapy has not been determined; however, only 2% (1/50) of patients who did not demonstrate at least a 25% decrease in tumor burden prior to the fourth course of treatment subsequently responded.

Special Handling:

• ONTAK must be brought to room temperature, up to 25° C (77°F), before preparing the dose. The vials may be thawed in the refriger-

ator or the rate should be reduced depending on the severity of the reaction. There is no clinical experience with prolonged infusion times (> 80 minutes).

The optimal duration of therapy has not been determined; however, only 2% (1/50) of patients who did not demonstrate at least a 25% decrease in tumor burden prior to the fourth course of treatment subsequently responded.

Special Handling:

• ONTAK must be brought to room temperature, up to 25° C (77°F), before preparing the dose. The vials may be thawed 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. ONTAK MUST NOT BE HEATED.

• The solution in the vial may be mixed by gentle swirling; DO NOT VIGOROUSLY SHAKE ONTAK SOLUTION.

• After thawing, a haze may be visible. This haze should clear when the solution is at room temperature.

• ONTAK solution must not be used unless the solution is clear, colorless and without visible particulate matter.

• ONTAK MUST NOT BE REFROZEN.

Preparation and Administration:

• USE APPROPRIATE ASEPTIC TECHNIQUE IN DILUTION AND ADMINISTRATION OF ONTAK.

• Prepare and hold diluted ONTAK in plastic syringes or soft plastic IV bags. DO NOT USE A GLASS CONTAINER because adsorption to glass may occur in the dilute state.

• The concentration of ONTAK must be at least 15 mcg/mL during all steps in the preparation of the solution for IV infusion. This is best accomplished by withdrawing the calculated dose from the vial(s) and injecting it into an empty IV infusion bag. FOR EACH 1 mL OF ONTAK FROM THE VIAL(S), NO MORE THAN 9 mL OF STERILE SALINE WITHOUT PRESERVATIVE SHOULD THEN BE ADDED TO THE IV BAG.

• The ONTAK dose should be infused over at least 15 minutes.

• ONTAK SHOULD NOT BE ADMINISTERED AS A BOLUS INJECTION.

• Do not physically mix ONTAK with other drugs.

• DO NOT ADMINISTER ONTAK THROUGH AN IN-LINE FILTER.

• Prepared solutions of ONTAK should be administered within 6 hours, using a syringe pump or IV infusion bag.

• Unused portions of ONTAK should be discarded immediately.

HOW SUPPLIED

ONTAK is supplied as:
150 mcg/mL sterile, frozen solution (300 mcg in 2 mL) in a sterile, single-use vial
NDC 64365-503-01, 6 vials in a package.

Store frozen at or below -10°C.

REFERENCES

1. Nakase K, Kita K, Nasu K, Ueda T, Tanaka I, Shirakawa S and Tsudo M. Differential expression of interleukin-2 receptor (α and β chain) in mature lymphoid neoplasms. *Amer. J. Hematol.* 1994; 46: 179-183.

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