In additional open clinical trials, the observed rate of reversal of acute renal allograft rejection was 92% (n=126) for ORTHOCLONE OKT3 therapy, ORTHOCLONE OKT3 was also effective in reversing acute renal allograft rejection in patients who were unresponsive to high-doses of steroids. The rate of reversal in acute cardiac allograft rejection was 90% (n=81) for ORTHOCLONE OKT3 and 83% for hepatic allograft rejection (n=164) in patients unresponsive to treatment with steroids.

Controlled randomized trials have not been conducted to evaluate the effectiveness of ORTHOCLONE OKT3 compared to conventional therapy as first line treatment for acute cardiac and hepatic allograft rejection.

INDICATIONS AND USAGE

ORTHOCLONE OKT3 is indicated for the treatment of acute allograft rejection in renal transplant patients.

ORTHOCLONE OKT3 is indicated for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

The use of other immunosuppressive agents used in conjunction with ORTHOCLONE OKT3 should be reduced to the lowest level compatible with an effective therapeutic response. (See: WARNINGS and ADVERSE EVENTS: Infections, Neoplasia; DOSAGE AND ADMINISTRATION)

CONTRAINDICATIONS

ORTHOCLONE OKT3 should not be given to patients who:

- have hypersensitivity to any of its monocomponent products; or
- have in (uncompensated) heart failure or in fluid overload, as evidenced by chest X-ray or a greater than 3 percent weight gain within the week prior to planned ORTHOCLONE OKT3 administration.

- have uncontrolled hypertension;
- are in (uncompensated) heart failure or in fluid overload, as evidenced by chest X-ray or a greater than 3 percent weight gain within the week prior to planned ORTHOCLONE OKT3 administration.

- are determined or suspected to be pregnant, or who are breast-feeding. (See: PRECAUTIONS: Pregnancy, Nursing Mothers)

WARNINGs

SEE BOXED WARNING

Cytokine Release Syndrome

Most patients develop an acute clinical syndrome [i.e., Cytokine Release Syndrome (CRS)] that has been attributed to the release of cytokines by activated lymphocytes or monocytes and is temporal-

ly associated with the administration of the first few doses of ORTHOCLONE OKT3 (typically, the first three doses). These ranges have been reported with mixed results due to both the self-limited, “flu-like” illness to a less frequently reported severe, life-threatening shock-like reaction, which may include serious cardiovascular and central nervous system manifestations. The outcome of treatment with ORTHOCLONE OKT3 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.

Anaphylaxis and anaphylactoid reactions may occur following administration of any dose or course of ORTHOCLONE OKT3. In addition, serious, occasionally life-threatening or lethal, systemic, cardiovascular, and central nervous system reactions have been reported following administration of ORTHOCLONE OKT3. These reactions are usually associated with the CD3 positive cells and characterized by release of pro-inflammatory cytokines. Clinical manifestations may be related to cytokines altering membrane permeability, rather than an active inflammatory process. The mechanism for this effect is not completely understood, but may involve the release of cytokines by activated lymphocytes or monocytes and is temporal-

ly associated with the administration of the first few doses of ORTHOCLONE OKT3 (typically, the first three doses). These ranges have been reported with mixed results due to both the self-limited, “flu-like” illness to a less frequently reported severe, life-threatening shock-like reaction, which may include serious cardiovascular and central nervous system manifestations. The outcome of treatment with ORTHOCLONE OKT3 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.

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Signs and symptoms of the aspecific meningitis syndrome described in association with the use of ORTHOCLONE OKT3 include: fever, headache, meningismus (stiff neck), and photophobia. Diagnosis is based on the development of the meningismus syndrome and other signs and symptoms of meningitis. Most patients with the aspecific meningitis syndrome had coexisting signs and symptoms of encephalopathy. Most patients with the aspecific meningitis syndrome had a benign course and recovered without any permanent sequelae or complications of meningitis. However, because meningitis is a frequent infection encountered in pediatric allograft recipients, and the immunosuppression associated with transplantation increases the risk of opportunistic infection, the mechanism responsible for any infection, fluid and electrolyte disturbance, etc.; with underlying vascular diseases; or who are receiving a medication concomitantly that may, by itself, affect the central nervous system. (See: WARNINGS and ADVERSE EVENTS: CNS and ANGIOEDEMA. ADVERSE EVENTS: Central Nervous System Events)

Serious and occasionally fatal, immediate (usually within 10 minutes) hypersensitivity reactions have been reported in patients treated with ORTHOCLONE OKT3. Severe, immediate onset (usually within 10 minutes) following administration of ORTHOCLONE OKT3 are probably due to acute hypersensitivity. If hypersensitivity is suspected, discontinue the drug immediately. (See: WARNINGS, ADVERSE EVENTS: Hypersensitivity Reactions)

Hypersensitivity to OKT3 may impair mental alertness and coordination and may effect the therapeutic response so as to reduce the potential for and severity of infections and malignant disorders. Since the potential for the development of lymphoproliferative disorders is related to the duration and magnitude of the host antibody response. Furthermore, immunosuppressive agents used concomitantly with ORTHOCLONE OKT3 may affect both the incidence and magnitude of the host antibody response. Additionally, microangiopathic changes (e.g., platelet destruction) may occur with OKT3 therapy. However, because meningitis is a frequent infection encountered in pediatric allograft recipients, and the immunosuppression associated with transplantation increases the risk of opportunistic infection, the mechanism responsible for any infection, fluid and electrolyte disturbance, etc.; with underlying vascular diseases; or who are receiving a medication concomitantly that may, by itself, affect the central nervous system. (See: WARNINGS and ADVERSE EVENTS: CNS and ANGIOEDEMA. ADVERSE EVENTS: Central Nervous System Events)

Approximately one to six months post-transplant, patients are at risk for viral infections [e.g., cytomegalovirus (CMV)]. In the pediatric transplant population, viral infections often include pathogens uncommon in adults, and are susceptible to developing primary infections from the grafted organ and/or blood products. Infection/Viral-Induced Lymphoproliferative Disorders: If infection or a viral induced lymphoproliferative disorder is suspected, an immediate onset (usually within 10 minutes) following administration of ORTHOCLONE OKT3 should be ruled out. (See: WARNINGS and ADVERSE EVENTS: Central Nervous System Events)

Serious allergic events, including anaphylactic or anaphylactoid reactions, have been reported in patients treated with ORTHOCLONE OKT3. Severe and occasionally fatal, immediate (usually within 10 minutes) hypersensitivity reactions have been reported in patients treated with ORTHOCLONE OKT3. Severe, immediate onset (usually within 10 minutes) following administration of ORTHOCLONE OKT3 are probably due to acute hypersensitivity. If hypersensitivity is suspected, discontinue the drug immediately. (See: WARNINGS, ADVERSE EVENTS: Hypersensitivity Reactions)

As with other immunosuppressive medications used in combination with ORTHOCLONE OKT3, it may be necessary to continue to use the same agent or another agent for a period of time; and, if appropriate, to reduce the dosage(s) of immunosuppressive drugs used concomitantly. In the initial clinical trials using doses of prednisone and azathioprine during ORTHOCLONE OKT3 therapy for renal allograft rejection, antibodies to ORTHOCLONE OKT3 were observed with an incidence of 21% (n=43) for IgG, 86% (n=43) for IgG and 29% (n=36) for IgE. The mean time for appearance of IgG antibodies was 20 ± 2 days (mean ± SD). Early IgG antibodies appeared towards the end of the second week of treatment in 3% (n=86) of the patients. Subsequent clinical experience has shown that the dose, duration, and type of immunosuppressive medications used in combination with ORTHOCLONE OKT3 may affect both the incidence and the severity of the antibodies formed (i.e., idiotype, isotopic, idiotypic).
should be given to a pregnant woman only if clearly needed. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus. This drug is not used in pregnant women. Nursing Mothers: It is not known whether ORTHOCLONE OKT3 is excreted in human milk.

Other Information

It is not known whether ORTHOCLONE OKT3 is excreted in human milk.

Adverse Events

Table 1: Adverse Events Reported in Clinical Trials

<table>
<thead>
<tr>
<th>Body System</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic Nervous System Disorders</td>
<td>7</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>7</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
</tr>
<tr>
<td>Lethargy</td>
<td>6</td>
</tr>
<tr>
<td>Pain, trunk</td>
<td>6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>77</td>
</tr>
<tr>
<td>Cardiovascular Disorders, General</td>
<td>4</td>
</tr>
<tr>
<td>Amythymia</td>
<td>4</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
</tr>
<tr>
<td>Hypotension</td>
<td>25</td>
</tr>
<tr>
<td>Pan, chest</td>
<td>14</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>19</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>32</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>32</td>
</tr>
<tr>
<td>Central &amp; Peripheral Nervous System Disorders</td>
<td>32</td>
</tr>
<tr>
<td>Convulsion</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
</tr>
<tr>
<td>Migraine</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal System Disorders</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
<td>32</td>
</tr>
<tr>
<td>Pain, abdominal</td>
<td>32</td>
</tr>
<tr>
<td>Pain, GI</td>
<td>32</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
</tr>
<tr>
<td>Hematopoietic Disorders</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>12</td>
</tr>
</tbody>
</table>

In the clinical randomized renal allograft rejection trial conducted before cyclosporine was marketed, the most common infections reported in patients treated with ORTHOCLONE OKT3 during the first 45 days following the first two doses in less than 2% of patients were cytomegalovirus (9% of patients, of which 30% of infections were severe), fungal infections (15% of patients, of which 30% were severe), and herpes simplex virus (8% of patients, of which 10% were severe). Other severe and life-threatening infections were gram-negative bacteria (8% of patients, of which 20% were severe), fungal infections (4% of patients, of which 75% were severe), and cytomegalovirus (3% of patients, of which 33% were severe). No other severe or life-threatening infections were reported during this period.

In a retrospective analysis of pediatric patients treated for acute hepatic rejection, the most common infections reported in patients treated with ORTHOCLONE OKT3 therapy were due to bacterial infections (25%), cytomegalovirus (15%), hepatitis A virus (10%), herpes simplex virus (15%), adenovirus (8%), and Epstein-Barr virus (8%). The overall rates of viral, fungal, and bacterial infections were similar in patients treated with ORTHOCLONE OKT3 (n = 53) and in patients whose rejection was refractory to conventional treatment alone (n = 52).

In another study involving 149 pediatric allograft recipients where 59 episodes of steroid-resistant rejection were treated with ORTHOCLONE OKT3, the incidence of invasive cytomegalovirus infection was higher in patients receiving ORTHOCLONE OKT3 than in those receiving steroids alone.

Clinical significant infections (e.g., pneumonia, sepsis, etc.) due to the pathogens have been reported.

Bacterial: Closstridium species (including perfringens), Corynebacterium, Enterococcus, Enterobacter aerogenes, Escherichia coli, Klebsiella species, Lactobacillus, Legionella, Listeria monocytogenes, Mycobacteria species, Nocardia asteroides, Proteus species, Providencia species, Pseudomonas aeruginosa, Sarnea species, Staphylococcus species, Streptococcus species, Yersinia enterocolitica, and other gram-negative bacteria.

Viral: cytomegalovirus* (CMV), Epstein-Barr virus* (EBV), herpes simplex virus* (HSV), hepatitis A virus, varicella zoster virus (VZV), adenovirus, enterovirus, respiratory syncytial virus (RSV), parainfluenza virus.

As a consequence of being a potent immunosuppressive, the incidence and severity of infections with ORTHOCLONE OKT3* in patients with high-risk pathogens, especially the herpes family of viruses, may be increased. (See WARNINGS: Infections)

Neoplasia

In patients treated with ORTHOCLONE OKT3, post-transplant lymphoproliferative disorders have ranged from lymphoproliferative to benign polyclonal B cell hyperplasias to malignant and often fatal monomorphic B cell lymphomas. In post-marketing experience, approximately one-third of the lymphomas reported were benign-lymphoid conditions where 59 episodes of steroid-resistant rejection were treated with ORTHOCLONE OKT3, the incidence of monomorphic B cell lymphomas dominated the clinical presentation, the majority of which were post-transplant lymphoproliferative disorders have ranged from lymphoproliferative to benign polyclonal B cell hyperplasias to malignant and often fatal monomorphic B cell lymphomas. In post-marketing experience, approximately one-third of the lymphomas reported were benign-lymphoid conditions

Other neoplasms reported less frequently in post-marketing follow-up include myeloma, leukemia, carcinoma of the breast, adenocarcinoma, cholangiocarcinoma, and recurrences of pre-existing neoplasms and renal cell carcinoma. (See WARNINGS: Neoplasia)

Hypersensitivity Reactions

Reported adverse reactions resulting from the formation of antibodies to ORTHOCLONE OKT3 have included neutralizing antibodies (immune complex) mediated syndromes and IgE-mediated reactions. Hypersensitivity reactions have ranged from a mild, self-limited rash or pruritus to severe, life-threatening anaphylactic reactions/shock or angioedema (including swelling of lips, eyelids, laryngeal edema and airway obstruction with hypoxia). (See WARNINGS: Anaphylactic Reactions)

Other hypersensitivity reactions have included: ineflectiveness of treatment, serum sickness, arthralgia, allergic interstitial nephritis, immune complex deposition resulting in glomerulonephritis, vasculitis (including temporal and renal), and eosinophilia.

Adverse Reactions by Body System

Adverse events reported in greater than or equal to 1% of clinical trial patients treated with ORTHOCLONE OKT3 (n=383) are shown in Table 1:

Other serious and occasionally fatal cardiorespiratory manifestations have been reported following the formation of antibodies to ORTHOCLONE OKT3 have included neutralizing antibodies (immune complex) mediated syndromes and IgE-mediated reactions. Hypersensitivity reactions have ranged from a mild, self-limited rash or pruritus to severe, life-threatening anaphylactic reactions/shock or angioedema (including swelling of lips, eyelids, laryngeal edema and airway obstruction with hypoxia). (See WARNINGS: Anaphylactic Reactions)

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Musculoskeletal System Disorders
Arthralgia
7
Myalgia
1
Psychiatric Disorders
Confusion
6
Depression
3
Nervousness
5
Somnolence
2
Renal Disorders
Abnormal Creatinine Concentration
6
Dysuria
16
Hypertension
26
Hypotonia
1
Orthostatic Hypotension
2
Pneumonia
1
Pulmonary Edema
1
Respiratory Congestion
4
Wheezing
6
Skin and Appendages Disorders
Pruritus
3
 Rash
7
Rash Erythematous
2
Special Senses
Photophobia
1
Tinnitus
7
White Cell and Reticuendothelial System Disorders
Leukopenia
7

Selected Adverse Events Reported in Clinical Trials (≤ 1% incidence, n=393):
Cardiovascular Disorders, General: Angina, Cardiac Arrest, Fluctuation in Blood Pressure, Heart Failure, Myocardial Infarction, Shock, Thrombosis.
Central & Peripheral Nervous System Disorders: Coma, Encephalopathy, Epilepsys, Hypotonia.
Gastrointestinal Disorders: Gastrointestinal Hemorrhage.
Hematopoietic Disorders: Coagulation Disorder, Lymphadenopathy, Lymphopenia.
Hepatobiliary: Hepatitis, SGOT Increased, SGPT Increased.
Psychiatric Disorders: Hallucinations, Mood Changes, Paranoia, Psychosis.
Renal Disorders: Anuria, Oliguria.
Respiratory System Disorders: Apnea, Pneumonitis.
Special Senses: Conjunctivitis, Hearing Decrease.

Worldwide Postmarketing Experience - Body Systems/Events Listed Alphabetically:
Body As a Whole, General Disorders: Fever (including spiking temperatures as high as 107°F), Flu-like Syndrome.
Cardiovascular Disorders: Cardiovascular Collapse, Hemodynamic Instability, Left Ventricular Dysfunction.
Gastrointestinal Disorders: Bowel Infarction.
Hematopoietic Disorders: Aplastic anemia, Arterial, Venous and Capillary Thrombosis of allografts and other vascular beds e.g., heart, lung, brain and bowel etc., Disseminated Intravascular Coagulation, Microangiopathic Hemolytic Anemia, Neutropenia, Pancytopenia.
Hepatobiliary: Hepatitis or Hepato-splenomegaly, usually secondary to viral infection or lymphoma.
Musculoskeletal Disorders: Arthritis, Arthralgia, Ache/Pain.
Renal Disorders: Azotemia, Abnormal Urinary Cytology including exfoliation of damaged lymphocytes, collecting duct cells and tubular casts, Delayed Graft Function, Renal Insufficiency/Renal Failure, usually transient and reversible and occasionally in association with Cytokine Release Syndrome.
Respiratory System Disorders: Adult Respiratory Distress Syndrome, Respiratory Arrest, Respiratory Failure.
Skin and Appendages: Erythema, Flushing, Stevens-Johnson Syndrome, Urticaria.
Special Senses: Blindness, Blurred Vision, Deafness, Diplopia, Otitis Media, Nasal and Ear Stuffiness, Papilledema.

OVERDOSAGE:
Symptoms of overdosage with ORTHOCLONE OKT3 may include hyperthermia, severe chills, myalgia, vomitting, diarrhea, edema, oliguria, pulmonary edema, and acute renal failure. A high incidence (5%) of microangiopathic hemolytic anemia/HUS syndrome in patients receiving 10 mg per day of ORTHOCLONE OKT3 was also reported. In the event of acute overdosage with ORTHOCLONE OKT3, the patient’s volume status should be assessed carefully. It is imperative, especially prior to the first few doses, that there be no clinical evidence of volume overload, uncontrolled hypertension, or uncompensated heart failure. Patients should have a clear chest X-ray and should not weigh more than 3% above their minimum weight during the week prior to injection.

To decrease the incidence and severity of Cytokine Release Syndrome, associated with the first dose of ORTHOCLONE OKT3, it is strongly recommended that methylprednisolone sodium succinate 8.0 mg/kg be administered intravenously 1 to 4 hours prior to the initial dose of ORTHOCLONE OKT3. Acetaminophen and antihistamines given concomitantly with ORTHOCLONE OKT3 may also help to reduce some early reactions. (See: WARNINGS and ADVERSE EVENTS: Cytokine Release Syndrome)

When using concomitant immunosuppressive drugs, the dose of each should be reduced to the lowest level compatible with an effective therapeutic response in order to reduce the potential for malignancy and infections. Maintenance immunosuppression should be reduced approximately three days prior to the cessation of ORTHOCLONE OKT3 therapy. (See: WARNINGS and ADVERSE EVENTS: Infection, Neoplasia)

Reduced T cell clearance or low plasma ORTHOCLONE OKT3 levels provide a basis for adjusting ORTHOCLONE OKT3 dosage or for discontinuing therapy. (See: WARNINGS: Anaphylactic Reactions; PRECAUTIONS: Laboratory Tests; ADVERSE EVENTS: Hypersensitivity Reactions)

ADMINISTRATION INSTRUCTIONS
1. Before administration, ORTHOCLONE OKT3 should be inspected for particulate matter and discoloration. Because ORTHOCLONE OKT3 is a protein solution, it may develop fine translu-
cent particles (shown not to affect potency).
2. No bacteriostatic agent is present in this product. Adhereance to aseptic technique is advised. Once the ampule is open, use immediately and discard the unused portion.
3. Prepare ORTHOCLONE OKT3 for injection by drawing solution into a syringe through a low protein-binding 0.2 or 0.22 micrometer (μm) filter. Detach filter and attach a new needle for a single intravenous (bolus) injection.
4. Because no data is available on compatibility of ORTHOCLONE OKT3 with other intravenous substances or additives, other medications/substances should not be added or infused simul-
taneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed with saline before and after injec-
tion of ORTHOCLONE OKT3.

5. Administer ORTHOCLONE OKT3 as a single intravenous (bolus) injection in less than one minute. Do not administer by intravenous infusion or in conjunction with other drug solutions.

HOW SUPPLIED
ORTHOCLONE OKT3 is supplied as a sterile solution in packages of 5 ampules (NDC 596761-101-01). Each 5 mL ampule contains 5 mg of muramotan-CD3.

Storage: Store in a refrigerator at 2° to 8°C (36° to 46°F). DO NOT FREEZE OR SHAKE.

REFERENCES

ORTHOBIOOTECH PRODUCTS L.P. Raritan, New Jersey 08869 ©OBPLP 2001 631-10-191-3 Revised March 2001