ORTHOCLONE OKT®3 Sterile Solution (murumonab-CD3) For Intravenous Use Only

WARNING:
Only physicians experienced in immunosuppressive therapy and management of solid organ transplant patients should use ORTHOCLONE OKT3 (muromonab-CD3). Patients treated 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.

Anaphylactic 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 have included: pulmonary edema, especially in patients with volume overload; shock, cardiovascular collapse, cardiac or respiratory arrest, seizures, coma, cerebral edema, herniation, blindness, and paralysis. Fluid status should be carefully monitored prior to and during ORTHOCLONE OKT3 administration. Pretreatment with methylprednisolone is recommended to minimize symptoms of Cytokine Release Syndrome. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events, Anaphylactic Reactions; DOSAGE AND ADMINISTRATION)

DESCRIPTION

ORTHOCLONE OKT3 (muromonab-CD3) Sterile Solution is a murine monoclonal antibody to the CD3 antigen of human T cells which functions as an immunosuppressant. It is for intravenous use only. The antibody is a biochemically purified IgG_{2a} immunoglobulin with a heavy chain of approximately 50,000 daltons and a light chain of approximately 25,000 daltons. It is directed to a glycoprotein with a molecular weight of 20,000 in the human T cell surface which is essential for T cell functions. Because it is a monoclonal antibody preparation, ORTHOCLONE OKT3 Sterile Solution is a homogeneous, reproducible antibody product with consistent, measurable reactivity to human T cells.

Each 5 mL ampule of ORTHOCLONE OKT3 Sterile Solution contains 5 mg (1 mg/mL) of muromonab-CD3 in a clear colorless solution which may contain a few fine translucent protein particles. Each ampule contains a buffered solution (pH 7.0 $\pm$ 0.5) of monobasic sodium phosphate (2.25 mg), dibasic sodium phosphate (9.0 mg), sodium chloride (43 mg), and polysorbate 80 (1.0 mg) in water for injection.

The proper name, muromonab-CD3, is derived from the descriptive term murine monoclonal antibody. The CD3 designation identifies the specificity of the antibody as the Cell Differentiation (CD) cluster 3 defined by the First International Workshop on Human Leukocyte Differentiation Antigens.

CLINICAL PHARMACOLOGY

ORTHOCLONE OKT3 reverses graft rejection, probably by blocking the function of T cells which play a major role in acute allograft rejection. ORTHOCLONE OKT3 reacts with and blocks the function of a 20,000 dalton molecule (CD3) in the membrane of human T cells that has been associated *in vitro* with the antigen recognition structure of T cells and is essential for signal transduction. In *in vitro* cytolytic assays, ORTHOCLONE OKT3 blocks both the generation and function of effector cells. Binding of ORTHOCLONE OKT3 to T lymphocytes results in early activation of T cells, which leads to cytokine release, followed by blocking T cell functions. After termination of ORTHOCLONE OKT3 therapy, T cell function usually returns to normal within one week.

In vivo, ORTHOCLONE OKT3 reacts with most peripheral blood T cells and T cells in body tissues, but has not been found to react with other hematopoietic elements or other tissues of the body.

A rapid and concomitant decrease in the number of circulating CD3 positive cells, including those that are CD2, CD4, or CD8 positive has been observed in patients studied within minutes after the administration of ORTHOCLONE OKT3. This decrease in the number of CD3 positive T cells results from the specific interaction between ORTHOCLONE OKT3 and the CD3 antigen on the surface of all T lymphocytes. T cell activation results in the release of numerous cytokines/lymphokines, which are felt to be responsible for many of the acute clinical manifestations seen following ORTHOCLONE OKT3 administration. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events)

While CD3 positive cells are not detectable between days two and seven, increasing numbers of circulating CD2, CD4, and CD8 positive cells have been observed. The presence of these CD2, CD4, and CD8 positive cells has not been shown to affect reversal of rejection. After termination of ORTHOCLONE OKT3 therapy, CD3 positive cells reappear rapidly and reach pre-treatment levels within a week. In some patients however, increasing numbers of CD3 positive cells have been observed prior to termination of ORTHOCLONE OKT3 therapy. This reappearance of CD3 positive cells has been attributed to the development of neutralizing antibodies to ORTHOCLONE OKT3, which in turn block its ability to bind to the CD3 antigen on T lymphocytes. (See: PRECAUTIONS: Sensitization)

Pediatric patients are known to have higher CD3 lymphocyte counts than adults. Pediatric patients receiving ORTHOCLONE OKT®3 therapy often require progressively higher doses of ORTHOCLONE OKT3 to achieve depletion of CD3 positive cells (<25 cells/mm^3) and ensure therapeutic ORTHOCLONE OKT3 serum concentrations (>800 ng/mL). (See: DOSAGE AND ADMINISTRATION; PRECAUTIONS: Laboratory Tests).

Serum levels of ORTHOCLONE OKT3 are measurable using an enzyme-linked immunosorbent assay (ELISA). During the initial clinical trials in renal allograft rejection, in patients treated with 5 mg per day for 14 days, mean serum trough levels of the drug rose over the first three days and then averaged 900 ng/mL on days 3 to 14. Serum concentrations measured daily during treatment with ORTHOCLONE OKT3 in renal, hepatic, and cardiac allograft recipients revealed that pediatric patients less than 10 years of age have higher levels than patients 10-50 years of age. Subsequent clinical experience has demonstrated that serum levels greater than or equal to 800 ng/mL of ORTHOCLONE OKT3 blocks the function of cytotoxic T cells *in vitro* and *in vivo*. 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; DOSAGE AND ADMINISTRATION)

Following administration of ORTHOCLONE OKT3 *in vivo*, leukocytes have been observed in cerebrospinal and peritoneal fluids. The mechanism for this effect is not completely understood, but probably is related to cytokines altering membrane permeability, rather than an active inflammatory process. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events).

CLINICAL STUDIES

Acute Renal Rejection:
In a controlled randomized clinical trial, ORTHOCLONE OKT3 was compared with conventional high-dose steroid therapy in reversing acute renal allograft rejection. In this trial, 122 evaluable patients undergoing acute rejection of cadaveric renal transplants were treated either with ORTHOCLONE OKT3 daily for a mean of 14 days, with concomitant lowering of the dosage of azathioprine and maintenance steroids (62 patients), or with conventional high-dose steroids (60 patients). ORTHOCLONE OKT3 reversed 94% of the rejections compared to a 75% reversal rate obtained with conventional high-dose steroid treatment (p=0.006). The one year Kaplan-Meier (actuarial) estimates of graft survival rates for these patients who had acute rejection were 62% and 45% for ORTHOCLONE OKT3 and steroid-treated patients, respectively (p=0.04). At two years the rates were 56% and 42%, respectively (p=0.06).

One- and two-year patient survivals were not significantly different between the two groups, being 85% and 75% for ORTHOCLONE OKT3 treated patients and 90% and 85% for steroid-treated patients.

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 rejections in 65% (n=225) of cases where steroids and lymphocyte immune globulin preparations were contraindicated or were not successful.

The effectiveness of ORTHOCLONE OKT3 for prophylaxis of renal allograft rejection has not been established.

Acute Cardiac or Hepatic Allograft Rejection:
ORTHOCLONE OKT3 was studied for use in reversing acute cardiac and hepatic allograft rejection in patients who are unresponsive to high-doses of steroids. The rate of reversal in acute cardiac allograft rejection was 90% (n = 61) and was 83% for hepatic allograft rejection (n = 124) 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 dosage 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:
- are hypersensitive to this or any other product of murine origin;
- have anti-mouse antibody titers $\geq$1:1000;
- 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;
- have uncontrolled hypertension;
- have a history of seizures, or are predisposed to seizures;
- 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 temporally associated with the administration of the first few doses of ORTHOCLONE OKT®3 (particularly, the first two to three doses). This clinical syndrome has ranged from a more frequently reported mild, 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 syndrome typically begins approximately 30 to 60 minutes after administration of a dose of ORTHOCLONE OKT3 (but may occur later) and may persist for several hours. The frequency and severity of this symptom complex is usually greatest with the first dose. With each successive dose of ORTHOCLONE OKT3, both the frequency and severity of the Cytokine Release Syndrome tends to diminish. Increasing the amount of ORTHOCLONE OKT3 or resuming treatment after a hiatus may result in a reappearance of the CRS.

Common clinical manifestations of CRS may include: high fever (often spiking, up to 107˚F), chills/rigors, headache, tremor, nausea/vomiting, diarrhea, abdominal pain, malaise, muscle/joint aches and pains, and generalized weakness. Less frequently reported adverse experiences include: minor dermatologic reactions (e.g., rash, pruritus, etc.) and a spectrum of often serious, occasionally fatal, cardiorespiratory and central nervous system adverse experiences.

Cardiorespiratory findings may include: dyspnea, shortness of breath, bronchospasm/wheezing, tachypnea, respiratory arrest/failure/distress, cardiovascular collapse, cardiac arrest, angina/myocardial infarction, chest pain/tightness, tachycardia (including ventricular), hypertension, hemodynamic instability, hypotension including profound shock, heart failure, pulmonary edema (cardiogenic and non-cardiogenic), adult respiratory distress syndrome, hypoxemia, apnea, and arrhythmias. (See: BOXED WARNING; PRECAUTIONS; ADVERSE EVENTS)

In the initial studies of renal allograft rejection, potentially fatal, severe pulmonary edema occurred in 5% of the initial 107 patients. Fluid overload was present before treatment in all of these cases. It occurred in none of the subsequent 311 patients treated with first-dose volume/weight restrictions. In subsequent trials and in post-marketing experience, severe pulmonary edema has occurred in patients who appeared to be euvolemic. The pathogenesis of pulmonary edema may involve all or some of the following: volume overload; increased pulmonary vascular permeability; and/or reduced left ventricular compliance/contractility. During the first 1 to 3 days of ORTHOCLONE OKT3 therapy, some patients have experienced an acute and transient decline in the glomerular filtration rate (GFR) and diminished urine output with a resulting increase in the level of serum creatinine. Massive release of cytokines appears to lead to reversible renal functional impairment and/or delayed renal allograft function. Similarly, transient elevations in hepatic transaminases have been reported following administration of the first few doses of ORTHOCLONE OKT3.

Patients at risk for more serious complications of CRS may include those with the following conditions: unstable angina; recent myocardial infarction or symptomatic ischemic heart disease; heart failure of any etiology; pulmonary edema of any etiology; any form of chronic obstructive pulmonary disease; intravascular volume overload or depletion of any etiology (e.g., excessive dialysis, recent intensive diuresis, blood loss, etc.); cerebrovascular disease; patients with advanced symptomatic vascular disease or neuropathy; a history of seizures; and septic shock. Efforts should be made to correct or stabilize background conditions prior to the initiation of therapy. (See: PRECAUTIONS)

Prior to administration of ORTHOCLONE OKT3, the patient's volume (fluid) status and a chest x-ray should be assessed to rule out volume overload, uncontrolled hypertension, or uncompensated heart failure. Patients should not weigh >3% above their minimum weight during the week prior to injection.

The Cytokine Release Syndrome is associated with increased serum levels of cytokines (e.g., TNF-α, IL-2, IL-6, IFN-γ) that peak between 1 and 4 hours following administration of ORTHOCLONE OKT3. The serum levels of cytokines and the manifestations of CRS may be reduced by pretreatment with 8 mg/kg of methylprednisolone (i.e., high-dose steroids), given 1 to 4 hours prior to administration of the first dose of ORTHOCLONE OKT3, and by closely following recommendations for dosage and treatment duration. (See: DOSAGE AND ADMINISTRATION). It is not known if corticosteroid pretreatment decreases organ damage and sequelae associated with CRS. For example, increased intracranial pressure and cerebral herniation have occurred despite pretreatment with currently recommended doses and schedules of methyprednisolone.

If any of the more serious presentations of the Cytokine Release Syndrome occur, intensive treatment including oxygen, intravenous fluids, corticosteroids, pressor amines, antihistamines, intubation, etc., may be required.

Central Nervous System Events

Seizures, encephalopathy, cerebral edema, aseptic meningitis, and headache have been reported, even following the first dose, during therapy with ORTHOCLONE OKT®3. Seizures, some accompanied by loss of consciousness or cardiorespiratory arrest, or death, have occurred independently or in conjunction with any of the neurologic syndromes described below.

A few cases of fatal cerebral herniations subsequent to cerebral edema have been reported. All patients, particularly pediatric patients, must be carefully evaluated for fluid retention and

hypertension before the initiation of ORTHOCLONE OKT3 therapy. Close monitoring for neurologic symptoms must be performed during the first twenty-four (24) hours following each of the first few doses of ORTHOCLONE OKT3 injection.

Patients should be closely monitored for convulsions and manifestations of encephalopathy, including: impaired cognition, confusion, obtundation, altered mental status, disorientation, auditory/visual hallucinations, psychosis (delirium, paranoia), mood changes (e.g., mania, agitation, combativeness, etc.), diffuse hypotonus, hyperreflexia, myoclonus, tremor, asterixis, involuntary movements, major motor seizures, lethargy/stupor/coma, and diffuse weakness. Approximately one-third of patients with a diagnosis of encephalopathy may have had coexisting aseptic meningitis syndrome.

Signs and symptoms of the aseptic meningitis syndrome described in association with the use of ORTHOCLONE OKT3 have included: fever, headache, meningismus (stiff neck), and photophobia. Diagnosis is confirmed by cerebrospinal fluid (CSF) analysis demonstrating leukocytosis with pleocytosis, elevated protein and normal or decreased glucose, with negative viral, bacterial, and fungal cultures. The possibility of infection should be evaluated in any immunosuppressed transplant patient with clinical findings suggesting meningitis. Approximately one-third of the patients with a diagnosis of aseptic meningitis had coexisting signs and symptoms of encephalopathy. Most patients with the aseptic meningitis syndrome had a benign course and recovered without any permanent sequelae during therapy or subsequent to its completion or discontinuation. However, because meningitis is a frequent infection encountered in pediatric allograft recipients, and the immunosuppression associated with transplantation increases the risk of opportunistic infection, pediatric patients with signs or symptoms suggestive of meningeal irritation while receiving ORTHOCLONE OKT3 should have lumbar punctures performed to rule out an infectious etiology. (See: PRECAUTIONS: Pediatric Use)

Signs or symptoms of encephalopathy, meningitis, seizures, and cerebral edema, with or without headache, typically have been reversible. Headache, aseptic meningitis, seizures, and less severe forms of encephalopathy resolved in most patients despite continued treatment with ORTHOCLONE OKT3. However, some events resulted in permanent neurologic impairment.

The following additional central nervous system events have each been reported: irreversible blindness, impaired vision, quadri- or paraparesis/plegia, cerebrovascular accident (hemiparesis/plegia), aphasia, transient ischemic attack, subarachnoid hemorrhage, palsy of the VI cranial nerve, hearing decrease, and deafness.

Patients who may be at greater risk for CNS adverse experiences include those: with known or suspected CNS disorders (e.g., history of seizure disorder, etc.); with cerebrovascular disease (small or large vessel); with conditions having associated neurologic problems (e.g., head trauma, uremia, 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, PRECAUTIONS and ADVERSE EVENTS: Cytokine Release Syndrome)

Anaphylactic Reactions

Serious and occasionally fatal, immediate (usually within 10 minutes) hypersensitivity (anaphylactic) reactions have been reported in patients treated with ORTHOCLONE OKT3. **Manifestations of anaphylaxis may appear similar to manifestations of the Cytokine Release Syndrome (described above). It may be impossible to determine the mechanism responsible for any systemic reaction(s).** Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release. Acute hypersensitivity reactions may be characterized by: cardiovascular collapse, cardiorespiratory arrest, loss of consciousness, hypotension/shock, tachycardia, tingling, angioedema (including laryngeal, pharyngeal, or facial edema), airway obstruction, bronchospasm, dyspnea, urticaria, and pruritus.

Serious allergic events, including anaphylactic or anaphylactoid reactions, have been reported in patients re-exposed to ORTHOCLONE OKT3 subsequent to their initial course of therapy. Pretreatment with antihistamines and/or steroids may not reliably prevent anaphylaxis in this setting. Possible allergic hazards of retreatment should be weighed against expected therapeutic benefits and alternatives. If a patient is retreated with ORTHOCLONE OKT3, it is particularly important that epinephrine and other emergency life-support equipment should be immediately available.

If hypersensitivity is suspected, discontinue the drug immediately; do not resume therapy or re-expose the patient to ORTHOCLONE OKT3. Serious acute hypersensitivity reactions may require emergency treatment with 0.3 mL to 0.5 mL aqueous epinephrine (1:1000 dilution) subcutaneously and other resuscitative measures including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See: PRECAUTIONS: Cytokine Release Syndrome vs. Anaphylactic Reactions; ADVERSE EVENTS: Hypersensitivity Reactions)

Consequences of Immunosuppression

Serious and sometimes fatal infections and neoplasias have been reported in association with all immunosuppressive therapies, including those regimens containing ORTHOCLONE OKT®3.

Infections: ORTHOCLONE OKT3 is usually added to immunosuppressive therapeutic regimens, thereby augmenting the degree of immunosuppression. This increase in the total amount of immunosuppression may alter the spectrum of infections observed and increase the risk, the severity, and the morbidity of infectious complications. During the first month post-transplant, patients are at greatest risk for the following infections: (1) those present prior to transplant, perhaps exacerbated by post-transplant immunosuppression; (2) infection conveyed by the donor organ; and (3) the usual post-operative urinary tract, intravenous line related, wound, or pulmonary infections due to bacterial pathogens. (See: ADVERSE EVENTS: Infections)

Approximately one to six months post-transplant, patients are at risk for viral infections [e.g., cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), etc.] which produce serious systemic disease and which also increase the overall state of immunosuppression.

Reactivation (1 to 4 months post-transplant) of EBV and CMV has been reported. When administration of an anti-lymphocyte antibody, including ORTHOCLONE OKT3, is followed by an immunosuppressive regimen including cyclosporine, there is an increased risk of reactivating CMV and impaired ability to limit its proliferation, resulting in symptomatic and disseminated disease. EBV infection, either primary or reactivated, may play an important role in the development of post-transplant lymphoproliferative disorders. (See: WARNINGS and ADVERSE EVENTS: Neoplasia)

In the pediatric transplant population, viral infections often include pathogens uncommon in adults, such as varicella zoster virus (VZV), adenovirus, and respiratory syncytial virus (RSV). A large proportion of pediatric patients have not been infected with the herpes viruses prior to transplantation and, therefore, are susceptible to developing primary infections from the grafted organ and/or blood products.

Anti-infective prophylaxis may reduce the morbidity associated with certain potential pathogens and should be considered for pediatric and other high-risk patients. Judicious use of immunosuppressive drugs, including type, dosage, and duration, may limit the risk and seriousness of some opportunistic infections. It is also possible to reduce the risk of serious CMV or EBV infection by avoiding transplantation of a CMV-seropositive (donor) and/or EBV-seropositive (donor) organ into a seronegative patient.

Neoplasia: As a result of depressed cell-mediated immunity from immunosuppressive agents, organ transplant patients have an increased risk of developing malignancies. This risk is evidenced almost exclusively by the occurrence of lymphoproliferative disorders, squamous cell carcinomas of the skin and lip, and sarcomas. In immunosuppressed patients, T cell cytotoxicity is impaired allowing for transformation and proliferation of EBV-infected B lymphocytes. Transformed B lymphocytes are thought to initiate oncogenesis, which ultimately culminates in the development of most post-transplant lymphoproliferative disorders. Patients, especially pediatric patients, with primary EBV infection may be at a higher risk for the development of EBV-associated lymphoproliferative disorders. Data support an association between the development of lymphoproliferative disorders at the time of active EBV infection and ORTHOCLONE OKT3 administration in pediatric liver allograft recipients. (See: ADVERSE EVENTS, Infections, Neoplasia).

Following the initiation of ORTHOCLONE OKT3 therapy, patients should be continuously monitored for evidence of lymphoproliferative disorders through physical examination and histological evaluation of any suspect lymphoid tissue. Close surveillance is advised, since early detection with subsequent reduction of total immunosuppression may result in regression of some of these lymphoproliferative disorders. Since the potential for the development of lymphoproliferative disorders is related to the duration and extent (intensity) of total immunosuppression, physicians are advised: to adhere to the recommended dosage and duration of ORTHOCLONE OKT3 therapy; to limit the number of courses of ORTHOCLONE OKT3 and other anti- T lymphocyte antibody preparations administered within a short period of time; and, if appropriate, to reduce the dosage(s) of immunosuppressive drugs used concomitantly to the lowest level compatible with an effective therapeutic response. (See: DOSAGE AND ADMINISTRATION)

A recent study examined the incidence of non-Hodgkin's lymphoma (NHL) among 45,000 kidney transplant recipients and over 7,500 heart transplant recipients. This study suggested that all transplant patients, regardless of the immunosuppressive regimen employed, are at increased risk of NHL over the general population. The relative risk was highest among those receiving the most aggressive regimens.

The long-term risk of neoplastic events in patients being treated with ORTHOCLONE OKT3 has not been determined.

PRECAUTIONS

General

When using combinations of immunosuppressive agents, the dose of each agent, including ORTHOCLONE OKT®3, should be reduced to the lowest level compatible with an effective therapeutic response so as to reduce the potential for and severity of infections and malignant transformations.

Fever: If the temperature of the patient exceeds 37.8°C (100°F), it should be lowered by antipyretics before administration of each dose of ORTHOCLONE OKT3. The possibility of infection should be evaluated.

Severe Cytokine Release Syndrome Versus Anaphylactic Reactions: **It may not be possible to distinguish between an acute hypersensitivity reaction (e.g., anaphylaxis, angioedema, etc.) and the Cytokine Release Syndrome. Potentially serious signs and symptoms having an 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; do not resume therapy or re-expose the patient** to ORTHOCLONE OKT3. Clinical manifestations beginning approximately 30 to 60 minutes (or later) following administration of ORTHOCLONE OKT3 are more likely cytokine-mediated. (See: WARNINGS: Cytokine Release Syndrome, Anaphylactic Reactions)

Central Nervous System Events: Since some seizures (and other serious central nervous system events) following ORTHOCLONE OKT3 administration have been life-threatening, anti-seizure precautions (e.g., an airway ready for use, if needed) should be taken. (See: WARNINGS and ADVERSE EVENTS: Central Nervous System Events).

Infection/Viral-Induced Lymphoproliferative Disorders: If infection or a viral induced lymphoproliferative disorder occurs, culture or biopsy as soon as possible, promptly institute appropriate anti-infective therapy, and (if possible) reduce/discontinue immunosuppressive therapy. (See: WARNINGS, ADVERSE EVENTS)

Low Protein-Binding Filter: Use a low protein-binding 0.2 or 0.22 micrometer (μm) filter to prepare the injections. (See: ADMINISTRATION INSTRUCTIONS)

Sensitization: ORTHOCLONE OKT3 is a mouse (immunoglobulin) protein that can induce human anti-mouse antibody production (i.e., sensitization) in some patients following exposure; a titer ≥1:1000 is a contraindication for use. (See: WARNINGS, ADVERSE EVENTS)

In the initial clinical trials using low 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 IgM, 86% (n=43) for IgG and 29% (n=35) for IgE. The mean time of 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 magnitude of the host antibody response. Furthermore, immunosuppressive agents used concomitantly with ORTHOCLONE OKT3 (i.e., steroids, azathioprine, prednisone, or cyclosporine) have altered the time course of anti-mouse antibody development and the specificity of the antibodies formed (i.e., idiotypic, isotypic, allotypic).

Thrombosis: As with other immunosuppressive therapies, arterial, venous, and capillary thromboses of allografts and other vascular beds (e.g., heart, lungs, brain, bowel, etc.) have been reported in patients treated with ORTHOCLONE OKT3. In addition, microangiopathic changes (e.g., platelet microthrombi) in the renal allograft associated in some patients with microangiopathic hemolytic anemia have been reported. This was observed in 5 of 93 (5%) patients receiving doses above the recommended dose. The relationship to dose remains uncertain; however, the relative risk appears to be greater with doses above the recommended dose. Patients with a history of thrombosis or underlying vascular disease should be given ORTHOCLONE OKT3 only when the potential benefits clearly outweigh the increased risks of therapy.

Information for Patients:

Patients should be advised:

- of the signs and symptoms associated with the Cytokine Release Syndrome and the potentially serious nature of this syndrome (e.g., systemic, cardiovascular, central nervous system events).
- to seek medical attention for skin rash, urticaria, rapid heart beat, respiratory distress, dysphagia, or any swelling suggesting an allergic reaction or angioedema.
- that ORTHOCLONE OKT3 may impair mental alertness and coordination and may effect the ability to operate an automobile or machinery.
- of other risks associated with the use of ORTHOCLONE OKT3. (See: BOXED WARNING; WARNINGS; PRECAUTIONS; ADVERSE EVENTS)

Laboratory Tests: The following tests should be monitored prior to and during ORTHOCLONE OKT®3 therapy:

- Renal: BUN, serum creatinine, etc.;
- Hepatic: transaminases, alkaline phosphatase, bilirubin;
- Hematopoietic: WBCs and differential, platelet count, etc.;
- Chest X-ray within 24 hours before initiating ORTHOCLONE OKT3 treatment to rule out heart failure or fluid overload.
- Blood Tests: Periodic assessment of organ system functions (renal, hepatic, and hematopoietic) should be performed.

During therapy with ORTHOCLONE OKT3: In adults, periodic monitoring to ensure plasma ORTHOCLONE OKT3 levels (≥800 ng/mL) or T cell clearance (CD3 positive T cells <25 cells/mm^3) is recommended. In pediatric patients, both plasma ORTHOCLONE OKT3 levels (≥800 ng/mL) and T cell clearance (CD3 positive T cells <25 cells/mm^3) should be monitored daily. (See: CLINICAL PHARMACOLOGY).

Carcinogenesis: Long-term studies have not been performed in laboratory animals to evaluate the carcinogenic potential of ORTHOCLONE OKT3; however, neoplasia has been reported in patients receiving this product. (See: WARNINGS and ADVERSE EVENTS: Neoplasia)

Pregnancy Category C: Animal reproductive studies have not been conducted with ORTHOCLONE OKT3. It is also not known whether ORTHOCLONE OKT3 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, ORTHOCLONE OKT3 is an IgG antibody and may cross the human placenta. The effect on the fetus of the release of cytokines and/or immunosuppression after treatment with ORTHOCLONE OKT3 is not known. ORTHOCLONE OKT3

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 hazard to the fetus. (See: CONTRAINDICATIONS, WARNINGS, and ADVERSE EVENTS)

Nursing Mothers: It is not known whether ORTHOCLONE OKT3 is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse events/oncogenesis shown for ORTHOCLONE OKT3 in human studies, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See: CONTRAINDICATIONS)

Pediatric Use: Safety and effectiveness have been established in infants (1 mo. up to 2 yr.); children (2 yr. up to 12 yr.); and adolescents (12 yr. up to 16 yr.). Use of ORTHOCLONE OKT3 in these age groups is supported by clinical studies that included adults and pediatric patients. In those studies, the safety and efficacy of ORTHOCLONE OKT3 in pediatric patients receiving renal or hepatic transplants was similar to that in the overall cohort. There were insufficient data to compare the safety and efficacy of ORTHOCLONE OKT3 in pediatric patients in a study of patients receiving cardiac transplants. Additional pharmacokinetic, pharmacodynamic, and clinical studies in infants, children, and adolescents have been reported in published literature.

Pediatric patients are known to have higher CD3 lymphocyte counts than adults; therefore, progressively higher doses of ORTHOCLONE OKT3 are often required to achieve therapeutic levels of lymphocyte clearance. (See: DOSAGE AND ADMINISTRATION)

Specific Safety Concerns in Pediatric Patients

Deaths due to Cerebral Herniation:
The postmarketing data base indicates that pediatric patients may be at increased risk of developing cerebral edema with or without herniation compared to adults. In the period between 1986 and 1996, twenty-five cases (6 in pediatric patients) of cerebral edema were identified with subsequent cerebral herniation and death in five cases (4 in pediatric patients). Herniation in the pediatric patients and one 19 year old subject occurred within a few hours to one day after the first dose (2.5 or 5 mg) of ORTHOCLONE OKT3 administered in the investigational setting for prophylaxis of renal allograft rejection. All pediatric patients and especially those receiving a renal allograft must be carefully evaluated for fluid retention and hypertension before the initiation of ORTHOCLONE OKT3 therapy (See: WARNINGS: Cytokine Release Syndrome; DOSAGE AND ADMINISTRATION: General). Patients should be closely monitored for neurologic symptoms during the first twenty four (24) hours following each of the first few doses of ORTHOCLONE OKT3 injection.

Other Serious Central Nervous System Adverse Events:
Other significant neurologic complications reported in pediatric transplant recipients receiving ORTHOCLONE OKT3 include status epilepticus, cerebral edema, diffuse encephalopathy, cerebritis, seizures, cortical dysfunction, and intracranial hemorrhage. Permanent neurologic impairments(e.g., blindness, deafness, paralysis) have been reported rarely. Because meningitis is a frequent infection encountered in pediatric allograft recipients, and the immunosuppression associated with transplantation increases the risk of opportunistic infection, patients with meningeal irritation following treatment with ORTHOCLONE OKT3 therapy should be evaluated with lumbar puncture as early as possible to rule out an infectious etiology.

Viral Infection:
The overall incidence of infections appeared to be similar in pediatric patients compared to the overall population studied. In the pediatric population, viral infections often include pathogens uncommon in adults, such as varicella zoster virus (VZV), adenovirus, enterovirus, parainfluenza virus, and respiratory syncytial virus (RSV). In addition, many viral diseases often manifest differently in pediatric patients than they do in adults. Because a large proportion of pediatric patients have not been infected by herpes viruses (e.g., EBV, HSV, CMV) prior to transplantation they may be more susceptible to acquiring primary infections from the grafted organ and/or blood products when immunosuppressed. Antiviral prophylactic therapy may be particularly useful in these high risk pediatric patients. (See: ADVERSE EVENTS: Infections)

Neoplasia:
Patients with primary EBV infection may be at higher risk for the development of EBV-associated lymphoproliferative disorders. There are data to support an association between the development of lymphoproliferative disorders at the time of active EBV infection and ORTHOCLONE OKT®3 administration in pediatric liver allograft recipients. Antiviral prophylactic therapy may be particularly useful in these high risk pediatric patients.

Gastrointestinal Fluid Losses:
Parenteral hydration may be required for gastrointestinal fluid loss secondary to diarrhea and/or vomiting resulting from the "Cytokine Release Syndrome".

Thrombosis:
Pediatric patients may be at an increased risk of thrombosis. Pediatric patients weighing less than 15 kg are at high-risk for hepatic artery thrombosis. Thrombosis has been reported in pediatric transplant recipients treated with ORTHOCLONE OKT3. A number of factors, including surgical technique, the presence of a hypercoaguable state, and the absence of prior dialysis experience may be relevant to the pathophysiology of the increased risk of thrombosis. (See: BOXED WARNING; WARNINGS; PRECAUTIONS; ADVERSE EVENTS; DOSAGE AND ADMINISTRATION).

ADVERSE EVENTS

Cytokine Release Syndrome

In controlled clinical trials for treatment of acute renal allograft rejection, patients treated with ORTHOCLONE OKT3 plus concomitant low-dose immunosuppressive therapy (primarily azathioprine and corticosteroids) were observed to have an increased incidence of adverse experiences during the first two days of treatment, as compared with the group of patients receiving azathioprine and high-dose steroid therapy. During this period the majority of patients experienced pyrexia (90%), of which 19% were 40.0˚C (104˚F) or above, and chills (59%). In addition, other adverse experiences occurring in 8% or more of the patients during the first two days of ORTHOCLONE OKT3 therapy included: dyspnea (21%), nausea (19%), vomiting (19%), chest pain (14%), diarrhea (14%), tremor (13%), wheezing (13%), headache (11%), tachycardia (10%), rigor (8%), and hypertension (8%). A similar spectrum of clinical manifestations has been observed in open clinical studies and in post-marketing experience involving patients treated with ORTHOCLONE OKT3 for rejection following renal, cardiac, and hepatic transplantation.

Additional serious and occasionally fatal cardiorespiratory manifestations have been reported following any of the first few doses. (See: WARNINGS: Cytokine Release Syndrome; ADVERSE EVENTS: Cardiovascular, Respiratory)

In the acute renal allograft rejection trials, potentially fatal pulmonary edema had been reported following the first two doses in less than 2% of the patients treated with ORTHOCLONE OKT3. Pulmonary edema was usually associated with fluid overload. However, post-marketing experience revealed that pulmonary edema has occurred in patients who appeared to be euvolemic, presumably as a consequence of cytokine-mediated increased vascular permeability ("leaky capillaries") and/or reduced myocardial contractility/compliance (i.e., left ventricular dysfunction). (See: WARNINGS: Cytokine Release Syndrome; DOSAGE AND ADMINISTRATION)

Infections

In the controlled randomized renal allograft rejection trial conducted before cyclosporine was marketed, the most common infections during the first 45 days of ORTHOCLONE OKT3 therapy were due to herpes simplex virus (27%) and cytomegalovirus (19%). Other severe and life-threatening infections were *Staphylococcus epidermidis* (5%), *Pneumocystis carinii* (3%), *Legionella* (2%), *Cryptococcus* (2%), *Serratia* (2%) and gram-negative bacteria (2%). The incidence of infections was similar in patients treated with ORTHOCLONE OKT3 and in patients treated with high-dose steroids.

In a clinical trial of acute hepatic allograft rejection, refractory to conventional treatment, the most common infections reported in patients treated with ORTHOCLONE OKT3 during the first 45 days of the study were cytomegalovirus (16% of patients, of which 43% 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-positive infections (9% of patients), gram-negative infections (8% of patients), viral infections (2% of patients), and *Legionella* (1% of patients). In another trial studying the use of ORTHOCLONE OKT®3 in patients with hepatic allografts, the incidence of fungal infections was 34% and infections with the herpes simplex virus was 31%.

In a clinical trial studying the use of ORTHOCLONE OKT3 in patients with acute cardiac rejection refractory to conventional treatment, the most common infections in the ORTHOCLONE OKT3 group reported during the first 45 days of the study were herpes simplex virus (5% 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 (47%), fungal infections (21%), cytomegalovirus (19%), 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 treated with steroids alone (n = 27). In another study of 149 pediatric liver allograft patients 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.

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

Bacterial: *Clostridium* 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, Serratia* species, *Staphylococcus* species, *Streptococcus* species, *Yersinia enterocolitica*, and other gram-negative bacteria.

Fungal: * *Aspergillus*, *Candida*, *Cryptococcus*, *Dermatophytes*.

Protozoa: *Pneumocystis carinii*, *Toxoplasma gondii*.

Viral: cytomegalovirus* (CMV), Epstein-Barr virus* (EBV), herpes simplex virus* (HSV), hepatitis viruses, 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 designated(*) 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 lymphadenopathy or benign polyclonal B cell hyperplasias to malignant and often fatal monoclonal B cell lymphomas. In post-marketing experience, approximately one-third of the lymphoproliferations reported were benign and two-thirds were malignant. Lymphoma types included: B cell, large cell, polyclonal, non-Hodgkin's, lymphocytic, T cell, Burkitt's. The majority were not histologically classified. Malignant lymphomas appear to develop early after transplantation, the majority within the first four months post-treatment. Many of these have been rapidly progressive. Some were fulminant, involving the allografted organ and were widely disseminated at the time of diagnosis. Carcinomas of the skin included: basal cell, squamous cell, sarcoma, melanoma, and keratoacanthoma. Other neoplasms infrequently reported include: multiple myeloma, leukemia, carcinoma of the breast, adenocarcinoma, cholangiocarcinoma, and recurrences of pre-existing hepatoma and renal cell carcinoma. (See: WARNINGS: Neoplasia)

Hypersensitivity Reactions

Reported adverse reactions resulting from the formation of antibodies to ORTHOCLONE OKT3 have included antigen-antibody (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 spasm and airway obstruction with hypoxia). (See: WARNINGS: Anaphylactic Reactions)

Other hypersensitivity reactions have included: ineffectiveness of treatment, serum sickness, arthritis, allergic interstitial nephritis, immune complex deposition resulting in glomerulonephritis, vasculitis (including temporal and retinal), 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=393) are shown in Table 1:

Table 1: Adverse Events Reported in Clinical Trials (≥1% incidence, n=393)

Body System	Incidence (%)
Autonomic Nervous System Disorders	
Diaphoresis	7
Vasodilation	7
Body as a Whole, General Disorders	
Anorexia	4
Asthenia	10
Chills	43
Fatigue	9
Lethargy	6
Malaise	5
Pain, trunk	6
Pyrexia	77
Cardiovascular Disorders, General	
Arrhythmia	4
Bradycardia	4
Hypertension	19
Hypotension	25
Pain, chest	9
Tachycardia	26
Vascular Occlusion	2
Central & Peripheral Nervous System Disorders	
Convulsions	1
Dizziness	6
Headache	28
Meningitis	1
Tremor	14
Gastrointestinal System Disorders	
Diarrhea	37
Nausea	32
Pain, abdominal	6
Pain, GI	7
Vomiting	25
Hematopoietic Disorders	
Anemia	2
Leukocytosis	1
Thrombocytopenia	2
Metabolic and Nutritional Disorders	
Edema	12

Musculoskeletal System Disorders	
Arthralgia	7
Myalgia	1
Psychiatric Disorders	
Confusion	6
Depression	3
Nervousness	5
Somnolence	2
Renal Disorders	
Renal Dysfunction	3
Respiratory System Disorders	
Abnormal Chest Sound	10
Dyspnea	16
Hyperventilation	7
Hypoxia	1
Pneumonia	1
Pulmonary Edema	2
Respiratory Congestion	4
Wheezing	6
Skin and Appendages Disorders	
Pruritus	7
Rash	14
Rash Erythematous	2
Special Senses	
Photophobia	1
Tinnitus	1
White Cell & Reticuloendothelial 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, Epilepsy, Hypotonia.
Gastrointestinal Disorders: Gastrointestinal Hemorrhage.
Hemapoietic 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.
Central & Peripheral Nervous System Disorders: Agitation, Aphasia, Asterixis, Cerebritis, Cerebral Edema, Cerebral Herniation, Cerebrovascular Accident, CNS Infection, CNS Malignancy, Cranial Nerve VI Palsy, Encephalitis, Hyperreflexia, Involuntary Movements, Intracranial Hemorrhage, Impaired Cognition, Myoclonus, Obnubilation, Paresis/plegia including quadriparesis/plegia, Status Epilepticus, Stupor, Transient Ischemic Attack, Vertigo.

In a post-marketing survey involving 214 renal transplant patients, the incidence of aseptic meningitis syndrome was 6%. Fever (89%), headache (44%), neck stiffness (14%), and photophobia (10%) were the most commonly reported symptoms; a combination of these four symptoms occurred in 5% of patients.

Between 1987 and 1992, 75 post-marketing reports have described seizures, averaging about 12 per year, and including 23 fatalities. More than two-thirds of these reports (53) were of domestic spontaneous origin, and their age and sex distributions were broad. Post-licensure reports generally provide insufficient data to allow accurate estimation of risk or of incidence.
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 Changes (e.g., platelet microthrombi), Microangiopathic Hemolytic Anemia, Neutropenia, Pancytopenia.
Hepatobiliary: Hepatitis or Hepato/splenomegaly, usually secondary to viral infection or lymphoma.
Musculoskeletal Disorders: Arthritis, Stiffness/Aches/Pains.
Renal Disorders: Azotemia, Abnormal Urinary Cytology including exfoliation of damaged lymphocytes, collecting duct cells and cellular 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 OKT®3 may include hyperthermia, severe chills, myalgia, vomiting, 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 should be carefully observed and given symptomatic and supportive treatment.

DOSAGE AND ADMINISTRATION

Adults

The recommended dose of ORTHOCLONE OKT3 for the treatment of acute renal, steroid-resistant cardiac, or steroid-resistant hepatic allograft rejection is 5 mg per day in a single (bolus) intravenous injection in less than one minute for 10 to 14 days. For acute renal rejection, treatment should begin upon diagnosis. For steroid-resistant cardiac or hepatic allograft rejection, treatment should begin when the treating physician deems a rejection has not been reversed by an adequate course of corticosteroid therapy. (See: CLINICAL PHARMACOLOGY; PRECAUTIONS: Sensitization, Laboratory Tests)

Pediatric Patients

The initial recommended dose is 2.5 mg per day in pediatric patients weighing less than or equal to 30 kg and 5 mg per day in pediatric patients weighing greater than 30 kg in a single (bolus) intravenous injection in less than one minute for 10 to 14 days. Daily increases in ORTHOCLONE OKT3 doses (i.e., 2.5 mg increments) may be required to achieve depletion of CD3 positive cells (<25 cells/mm^3) and ensure therapeutic ORTHOCLONE OKT3 serum concentrations (> 800 ng/mL). Pediatric patients may require augmentation of the ORTHOCLONE OKT3 dose. For acute renal rejection, treatment should begin upon diagnosis. For steroid-resistant cardiac or hepatic allograft rejection, treatment should begin when the treating physician deems a rejection has not been reversed by an adequate course of corticosteroid therapy. (See: CLINICAL PHARMACOLOGY; PRECAUTIONS: Laboratory Tests; Pediatric Use)

General

For the first few doses, patients should be monitored in a facility equipped and staffed for cardiopulmonary resuscitation (CPR). Patients receiving subsequent doses of ORTHOCLONE OKT3, should also be monitored in a facility equipped and staffed for CPR. Vital signs should be monitored frequently. Patients receiving ORTHOCLONE OKT3 should also be carefully monitored for signs and symptoms of Cytokine Release Syndrome, particularly after the first few doses but also after a treatment hiatus with resumption of therapy. The patient's temperature should be lowered to <37.8°C (100°F) before the administration of any dose of ORTHOCLONE OKT3.

Prior to administration of 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 resumed approximately three days prior to the cessation of ORTHOCLONE OKT®3 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 translucent particles (shown not to affect potency).
2. No bacteriostatic agent is present in this product. Adherence to aseptic technique is advised. Once the ampule is opened, 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 simultaneously 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 injection 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 59676-101-01). Each 5 mL ampule contains 5 mg of muromonab-CD3.

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

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ORTHO BIOTECH PRODUCTS, L.P.
Raritan, New Jersey 08869
U.S.A.

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