[redacted]

Roche

ZENAPAX®
(Daclizumab)

STERILE CONCENTRATE FOR INJECTION

WARNING:

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe ZENAPAX® (Daclizumab). The physician responsible for ZENAPAX administration should have complete information requisite for the follow-up of the patient. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources.

DESCRIPTION: ZENAPAX® (Daclizumab) is an immunosuppressive, humanized IgG1 monoclonal antibody produced by recombinant DNA technology that binds specifically to the alpha subunit (p55 alpha, CD25, or Tac subunit) of the human high-affinity interleukin-2 (IL-2) receptor that is expressed on the surface of activated lymphocytes.

Daclizumab is a composite of human (90%) and murine (10%) antibody sequences. The human sequences were derived from the constant domains of human IgG1 and the variable framework regions of the Eu myeloma antibody. The murine sequences were derived from the complementarity-determining regions of a murine anti-Tac antibody. The molecular weight predicted from DNA sequencing is 144 kilodaltons.

ZENAPAX 25 mg/5mL is supplied as a clear, sterile, colorless concentrate for further dilution and intravenous administration. Each milliliter of ZENAPAX contains 5 mg of Daclizumab and 3.6 mg sodium phosphate monobasic monohydrate, 11 mg sodium phosphate dibasic heptahydrate, 4.6 mg sodium chloride, 0.2 mg polysorbate 80 and may contain hydrochloric acid or sodium hydroxide to adjust the pH to 6.9. No preservatives are added.

CLINICAL PHARMACOLOGY: *Mechanism of Action:* Daclizumab functions as an IL-2 receptor antagonist that binds with high-affinity to the Tac subunit of the high-affinity IL-2 receptor complex and inhibits IL-2 binding. Daclizumab binding is highly specific for Tac, which is expressed on activated but not resting lymphocytes. Administration of ZENAPAX inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

While in the circulation, ZENAPAX impairs the response of the immune system to antigenic challenges. Whether the ability to respond to repeated or ongoing challenges with those antigens returns to normal after ZENAPAX is cleared is unknown (see PRECAUTIONS).

Pharmacokinetics: In clinical trials involving renal allograft patients treated with a 1 mg/kg IV dose of ZENAPAX every 14 days for a total of five doses, peak serum concentration (mean ± SD) rose between the first dose (21 ± 14 µg/mL) and fifth dose (32 ± 22 µg/mL). The mean trough serum concentration before the fifth dose was 7.6 ± 4.0 µg/mL. In vitro and in vivo data suggest that serum levels of 5 to 10 µg/mL are necessary for saturation of the Tac subunit of the IL-2 receptors to block the responses of activated T lymphocytes.

Population pharmacokinetic analysis of the data using a two-compartment open model gave the following values for a reference patient (45-year-old male Caucasian patient with a body weight of 80 kg and no proteinuria): systemic clearance = 15 mL/hour, volume of central compartment = 2.5 liter, volume of peripheral compartment = 3.4 liter. The estimated terminal elimination half-life for the reference patient was 20 days (480 hours), which is similar to the terminal elimination half-life for human IgG (18 to 23 days). Bayesian estimates of terminal elimination half-life ranged from 11 to 38 days for the 123 patients included in the population analysis.

The influence of body weight on systemic clearance supports the dosing of ZENAPAX on a milligram per kilogram (mg/kg) basis. For patients studied, this dosing maintained drug exposure within 30% of the reference exposure. Covariate analyses showed that no dosage adjustments based on age, race, gender or degree of proteinuria, are required for renal allograft patients. The estimated interpatient variability (percent coefficient of variation) in systemic clearance and central volume of distribution were 15% and 27%, respectively.

Pharmacodynamics: At the recommended dosage regimen, Daclizumab saturates the Tac subunit of the IL-2 receptor for approximately

120 days post-transplant. The duration of clinically significant IL-2 receptor blockade after the recommended course of ZENAPAX is not known. No significant changes to circulating lymphocyte numbers or cell phenotypes were observed by flow cytometry. Cytokine release syndrome has not been observed after ZENAPAX administration.

CLINICAL STUDIES: The safety and efficacy of ZENAPAX for the prophylaxis of acute organ rejection in adult patients receiving their first cadaveric kidney transplant were assessed in two randomized, double-blind, placebo-controlled, multicenter trials. These trials compared a dose of 1.0 mg/kg of ZENAPAX with placebo when each was administered as part of standard immunosuppressive regimens containing either cyclosporine and corticosteroids (double-therapy trial, no US sites) or cyclosporine, corticosteroids, and azathioprine (triple-therapy trial, predominantly US sites) to prevent acute renal allograft rejection. ZENAPAX dosing was initiated within 24 hours pretransplant, with subsequent doses given every 14 days for a total of five doses.

The primary efficacy endpoint of both trials was the proportion of patients who developed a biopsy-proven acute rejection episode within the first 6 months following transplantation. As shown in Table 1, this incidence was significantly lower in the ZENAPAX-treated group in both the double-therapy and triple-therapy trials.

No difference in patient survival was observed in the triple-therapy study between ZENAPAX- and placebo-treated patients. Treatment with ZENAPAX was associated with better patient survival at 1 year post-transplant in the double-therapy study.

The incidence of delayed graft function was no different between placebo-treated and ZENAPAX-treated patients in either study. No difference in graft function was observed 1 year post-transplant in either study between placebo-treated and ZENAPAX-treated patients.

In a randomized, double-blind study, ZENAPAX (50 patients) or placebo (25 patients) was added to an immunosuppressive regimen of cyclosporine, mycophenolate mofetil, and steroids to assess tolerability, pharmacokinetics, and drug interactions. The addition of ZENAPAX to an immunosuppressive regimen of cyclosporine, mycophenolate mofetil, and steroids did not result in an increased incidence of adverse events or a change in the types of adverse events reported. The incidence of the combined endpoint of biopsy-proven or clinically presumptive acute rejection was 20% (5 of 25 patients) in the placebo group and 12% (6 of 50 patients) in the ZENAPAX group. Although numerically lower, the difference in acute rejection was not significant.

INDICATION AND USAGE: ZENAPAX is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

CONTRAINDICATION: ZENAPAX is contraindicated in patients with known hypersensitivity to Daclizumab or to any components of this product.

WARNINGS: See Boxed WARNING.

ZENAPAX should be administered under qualified medical supervision. Patients should be informed of the potential benefits of therapy and the risks associated with administration of immunosuppressive therapy.

While the incidence of lymphoproliferative disorders and opportunistic infections, in the limited clinical trial experience, was no higher in ZENAPAX-treated patients compared with placebo-treated patients, patients on immunosuppressive therapy are at increased risk for developing lymphoproliferative disorders and opportunistic infections and should be monitored accordingly.

Anaphylactoid reactions following the administration of ZENAPAX have not been observed but can occur following the administration of proteins. Medications for the treatment of severe hypersensitivity reactions should, therefore, be available for immediate use.

PRECAUTIONS: *General:* It is not known whether ZENAPAX use will have a long-term effect on the ability of the immune system to respond to antigens first encountered during ZENAPAX-induced immunosuppression.

Re-administration of ZENAPAX after an initial course of therapy has not been studied in humans. The potential risks of such re-administration, specifically those associated with immunosuppression and/or the occurrence of anaphylaxis/anaphylactoid reactions, are not known.

Immunogenicity: Low titers of anti-idiotype antibodies to Daclizumab were detected in the ZENAPAX-treated patients with an overall incidence of 8.4%. No antibodies that affected efficacy, safety, serum Daclizumab levels or any other clinically relevant parameter examined were detected.

Table 1. Efficacy Parameters

	Triple-therapy Regimen (cyclosporine, corticosteroids, and azathioprine)			Double-therapy Regimen (cyclosporine and corticosteroids)		
	Placebo (N=134)	ZENAPAX (N=126)	p-value	Placebo (N=134)	ZENAPAX (N=141)	p-value
Primary Endpoint						
Incidence of biopsy-proven acute rejection at 6 months						
No. of patients	47 (35%)	28 (22%)	0.03	63 (47%)	39 (28%)	0.001
Secondary Endpoints						
Incidence of biopsy-proven acute rejection at 1 year						
No. of patients	51 (38%)	35 (28%)	0.09	65 (49%)	39 (28%)	<0.001
Patient survival at 1 year post-transplant						
No. of patients	129 (96%)	123 (98%)	0.51	126 (94%)	140 (99%)	0.01
Graft survival at 1 year post-transplant						
No. of patients with functioning graft	121 (90%)	120 (95%)	0.08	111 (83%)	124 (88%)	0.30

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Drug Interactions: The following medications have been administered in clinical trials with ZENAPAX with no incremental increase in adverse reactions: cyclosporine, mycophenolate mofetil, ganciclovir, acyclovir, azathioprine, and corticosteroids. Very limited experience exists with the use of ZENAPAX concomitantly with tacrolimus, muromonab-CD3, antithymocyte globulin, and antilymphocyte globulin.

In renal allograft recipients treated with ZENAPAX and mycophenolate mofetil, no pharmacokinetic interaction between Daclizumab and mycophenolic acid, the active metabolite of mycophenolate mofetil, was observed.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies to evaluate the carcinogenic potential of ZENAPAX have not been performed. ZENAPAX was not genotoxic in the Ames or the V79 chromosomal aberration assays, with or without metabolic activation. The effect of ZENAPAX on fertility is not known, because animal reproduction studies have not been conducted with ZENAPAX (see WARNINGS and ADVERSE REACTIONS).

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with ZENAPAX. Therefore, it is not known whether ZENAPAX can cause fetal harm when administered to pregnant women or can affect reproductive capacity. In general, IgG molecules are known to cross the placental barrier. ZENAPAX should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should use effective contraception before beginning ZENAPAX therapy, during therapy, and for 4 months after completion of ZENAPAX therapy.

Nursing Mothers: It is not known whether ZENAPAX is excreted in human milk. Because many drugs are excreted in human milk, including human antibodies, and because of the potential for adverse reactions, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: No adequate and well-controlled studies have been completed in pediatric patients. The preliminary results of an ongoing safety and pharmacokinetic study (N=25) in pediatric patients (median age: 12 years of age, range: 11 months to 17 years of age; 11 months to 5 years = 7 patients; 6 years to 12 years = 6 patients; 13 years to 17 years = 12 patients) treated with ZENAPAX in addition to standard immunosuppressive agents including mycophenolate mofetil, cyclosporine, tacrolimus, azathioprine, and corticosteroids indicate that the most frequently reported adverse events were hypertension (48%), post-operative (post-traumatic) pain (44%), diarrhea (36%), and vomiting (32%). The reported rates of hypertension and dehydration were higher for pediatric patients than for adult patients. It is not known whether the immune response to vaccines, infection, and other antigenic stimuli administered or encountered during ZENAPAX therapy is impaired or whether such response will remain impaired after ZENAPAX therapy.

The preliminary pharmacokinetic results from this ongoing study in pediatric patients indicate Daclizumab serum levels (N=6) appear to be somewhat lower in pediatric renal transplant patients than in adult transplant patients administered the same dosing regimen. However, Daclizumab levels in these pediatric patients were sufficient to saturate the Tac subunit of the IL-2 receptor on lymphocytes as measured by flow cytometry (N=24). The Tac subunit of the IL-2 receptor was saturated immediately after the first dose of 1.0 mg/kg of Daclizumab and remained saturated for at least the first 3 months post-transplant. Saturation of the Tac subunit of the IL-2 receptor was similar to that observed in adult patients receiving the same dose regimen.

Geriatric Use: Clinical studies of ZENAPAX did not include sufficient numbers of subjects age 65 and older to determine whether they respond differently from younger subjects. Caution must be used in giving immunosuppressive drugs to elderly patients.

ADVERSE REACTIONS: The safety of ZENAPAX was determined in four clinical studies, three of which were randomized controlled clinical trials, in 629 patients receiving renal allografts of whom 336 received ZENAPAX and 293 received placebo. All patients received concomitant cyclosporine and corticosteroids.

ZENAPAX did not appear to alter the pattern, frequency or severity of known major toxicities associated with the use of immunosuppressive drugs.

Adverse events were reported by 95% of the patients in the placebo-treated group and 96% of the patients in the ZENAPAX-treated group. The proportion of patients prematurely withdrawn from the combined studies because of adverse events was 8.5% in the placebo-treated group and 8.6% in the ZENAPAX-treated group.

ZENAPAX did not increase the number of serious adverse events observed compared with placebo. The most frequently reported adverse events were gastrointestinal disorders, which were reported with equal frequency in ZENAPAX- (67%) and placebo-treated (68%) patient groups.

The incidence and types of adverse events were similar in both placebo-treated and ZENAPAX-treated patients. The following adverse events occurred in ≥5% of ZENAPAX-treated patients. These events included: *Gastrointestinal System:* constipation, nausea, diarrhea, vomiting, abdominal pain, pyrosis, dyspepsia, abdominal distention, epigastric pain not food-related; *Metabolic and Nutritional:* edema extremities, edema; *Central and Peripheral Nervous System:* tremor, headache, dizziness; *Urinary System:* oliguria, dysuria, renal tubular necrosis; *Body as a Whole — General:* post-traumatic pain, chest pain, fever, pain, fatigue; *Autonomic Nervous System:* hypertension, hypotension, aggravated hypertension; *Respiratory System:* dyspnea, pulmonary edema, coughing; *Skin and Appendages:* impaired wound healing without infection, acne; *Psychiatric:* insomnia; *Musculoskeletal System:* musculoskeletal pain, back pain; *Heart Rate and Rhythm:* tachycardia; *Vascular Extracardiac:* thrombosis; *Platelet, Bleeding and Clotting Disorders:* bleeding; *Hemic and Lymphatic:* lymphocele.

The following adverse events occurred in <5% and ≥2% of ZENAPAX-treated patients. These included: *Gastrointestinal System:* flatulence, gastritis, hemorrhoids; *Metabolic and Nutritional:* fluid overload, diabetes mellitus, dehydration; *Urinary System:* renal damage, hydronephrosis, urinary tract bleeding, urinary tract disorder, renal insufficiency; *Body as a Whole — General:* shivering, generalized weakness; *Central and Peripheral Nervous System:* urinary retention, leg cramps, prickly sensation; *Respiratory System:* atelectasis, congestion, pharyngitis, rhinitis, hypoxia, rales, abnormal breath sounds, pleural effusion; *Skin and Appendages:* pruritus, hirsutism, rash, night sweats, increased sweating; *Psychiatric:* depression, anxiety; *Musculoskeletal System:* arthralgia, myalgia; *Vision:* vision blurred; *Application Site:* application site reaction.

Incidence of Malignancies: One year after treatment, the incidence of malignancies was 2.7% in the placebo group compared with 1.5% in the ZENAPAX group. Addition of ZENAPAX did not increase the number of post-transplant lymphomas, which occurred with a frequency of <1% in both placebo-treated and ZENAPAX-treated groups.

Hyperglycemia: No differences in abnormal hematologic or chemical laboratory test results were seen between placebo-treated and ZENAPAX-treated groups with the exception of fasting blood glucose. Fasting blood glucose was measured in a small number of placebo- and ZENAPAX-treated patients. A total of 16% (10 of 64 patients) of placebo-treated and 32% (28 of 88 patients) of ZENAPAX-treated patients had high fasting blood glucose values. Most of these high values occurred either on the first day post-transplant when patients received high doses of corticosteroids or in patients with diabetes.

Incidence of Infectious Episodes: The overall incidence of infectious episodes, including viral infections, fungal infections, bacteremia and septicemia, and pneumonia, was not higher in ZENAPAX-treated patients than in placebo-treated patients. The types of infections reported were similar in both the ZENAPAX-treated and the placebo-treated groups. Cytomegalovirus infection was reported in 16% of the patients in the placebo group and 13% of the patients in the ZENAPAX group. One exception was cellulitis and wound infections, which occurred in 4.1% of placebo-treated and 8.4% of ZENAPAX-treated patients. At 1 year post-transplant, 7 placebo patients and only 1 ZENAPAX-treated patient had died of an infection.

OVERDOSAGE: There have not been any reports of overdoses with ZENAPAX. A maximum tolerated dose has not been determined in patients. A dose of 1.5 mg/kg has been administered to bone marrow transplant recipients without any associated adverse events.

DOSAGE AND ADMINISTRATION: ZENAPAX is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. The recommended dose for ZENAPAX is 1.0 mg/kg. The calculated volume of ZENAPAX should be mixed with 50 mL of sterile 0.9% sodium chloride solution and administered via a peripheral or central vein over a 15-minute period.

Based on the clinical trials, the standard course of ZENAPAX therapy is five doses. The first dose should be given no more than 24 hours before transplantation. The four remaining doses should be given at intervals of 14 days.

No dosage adjustment is necessary for patients with severe renal impairment. No dosage adjustments based on other identified covariates (age, gender, proteinuria, race) are required for renal allograft patients. No data are available for administration in patients with severe hepatic impairment.

Instructions for Administration:

- ZENAPAX IS NOT FOR DIRECT INJECTION. The calculated volume should be diluted in 50 mL of sterile 0.9% sodium chloride solution before intravenous administration to patients. When mixing the solution, gently invert the bag in order to avoid foaming; DO NOT SHAKE.
- Parenteral drug products should be inspected visually for particulate matter and discoloration before administration. If particulate matter is present or the solution colored, do not use.
- Care must be taken to assure sterility of the prepared solution, since the drug product does not contain any antimicrobial preservative or bacteriostatic agents.
- ZENAPAX is a colorless solution provided as a single-use vial; any unused portion of the drug should be discarded.
- Once the infusion is prepared, it should be administered intravenously within 4 hours. If it must be held longer, it should be refrigerated between 2° to 8°C (36° to 46°F) for up to 24 hours. After 24 hours, the prepared solution should be discarded.
- No incompatibility between ZENAPAX and polyvinyl chloride or polyethylene bags or infusion sets has been observed. No data are available concerning the incompatibility of ZENAPAX with other drug substances. However, other drug substances should not be added or infused simultaneously through the same intravenous line.

HOW SUPPLIED: ZENAPAX is supplied in single-use glass vials. Each vial contains 25 mg of Daclizumab in 5 mL of solution (NDC 0004-0501-09). Vials should be stored between the temperatures of 2° to 8°C (36° to 46°F); do not shake or freeze. Protect undiluted solution against direct light. Diluted medication is stable for 24 hours at 4°C or for 4 hours at room temperature.

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