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Daclizumab (Zenapax)

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Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug. Rates observed in clinical studies may not reflect those observed in clinical practice. Adverse reaction information obtained in clinical trials does, however, provide a basis for identifying adverse events that appear to be related to drug use and for approximating the rate of occurrence.

The safety of ZENAPAX (daclizumab) was determined in four clinical studies of renal allograft rejection, three of which were randomized controlled clinical trials, in 629 patients receiving renal allografts of whom 336 received ZENAPAX (daclizumab) and 293 received placebo. All patients received concomitant cyclosporine and corticosteroids. In these clinical trials, ZENAPAX (daclizumab) did not appear to alter the pattern, frequency or severity of known major toxicities associated with the use of immunosuppressive drugs.

The use of ZENAPAX (daclizumab) was associated with a higher incidence of mortality when compared to placebo in a large (n=434) randomized controlled study).**WARNINGS and Incidence of Infectious Episodes**of patients receiving cardiac transplants (see

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 The proportion of patients prematurely withdrawn from the combined studies because of adverse events was 8.5% in the placebo-treated group and 8.6% in the group treated with ZENAPAX (daclizumab) .

ZENAPAX (daclizumab) 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 (daclizumab) - (67%) and placebo-treated (68%) patient groups.

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

The following adverse events occurred in < 5% and ? 2% of patients treated with ZENAPAX (daclizumab) . These included: Gastrointestinal System: flatulence, gastritis, hemorrhoids;

renal damage, hydronephrosis, urinary tract bleeding, urinary tract ***Urinary System:*** fluid overload, diabetes mellitus, dehydration; ***Metabolic and Nutritional:*** urinary retention, leg ***Central and Peripheral Nervous System:*** shivering, generalized weakness;***Body as a Whole - General:*** disorder, renal insufficiency; ***Skin and*** atelectasis, congestion, pharyngitis, rhinitis, hypoxia, rales, abnormal breath sounds, pleural effusion;***Respiratory System:*** cramps, prickly sensation; ***Vision:*** arthralgia, myalgia;***Musculoskeletal System:*** depression, anxiety;***Psychiatric:*** pruritus, hirsutism, rash, night sweats, increased sweating; ***Appendages:*** application site reaction. ***Application Site:*** vision blurred;

Incidence of Malignancies

One and 3 years posttransplant, the incidence of malignancies was 2.7% and 7.8%, respectively, in the placebo group compared with 1.5% and 6.4%, respectively, in the ZENAPAX (daclizumab) group. Addition of ZENAPAX (daclizumab) did not increase the number of posttransplant lymphomas up to 3 years posttransplant. Lymphomas occurred at a frequency of ? 1.5% in both placebo-treated and ZENAPAX (daclizumab) -treated groups.

Hyperglycemia

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

treated with ZENAPAX (daclizumab) than in placebo-treated patients in trials of renal transplantation. In a large randomized study of ZENAPAX (daclizumab) used for the prevention of allograft rejection in patients receiving cardiac allografts, more patients receiving ZENAPAX (daclizumab) experienced severe or fatal infections after 12 months of therapy when compared to those receiving placebo (10% vs 7%, respectively). The risks of infection or death may be increased in patients).**WARNINGS**receiving concomitant anti-lymphocyte antibody therapy (see

The types of infections reported in trials of renal transplantation were similar in both the ZENAPAX (daclizumab) -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 (daclizumab) group. One exception was cellulitis and wound infections, which occurred in 4.1% of placebo-treated patients and 8.4% of patients treated with ZENAPAX (daclizumab) . At 1 year posttransplant, 7 placebo patients and 1 patient treated with ZENAPAX (daclizumab) had died of an infection. At 3 years posttransplant, 8 placebo patients and 4 patients treated with ZENAPAX (daclizumab) had died of infection.

Immunogenicity

Low titers of anti-idiotype antibodies to daclizumab were detected in the adult patients treated with ZENAPAX (daclizumab) with an overall incidence of 14%. The incidence of anti-daclizumab antibodies observed in the pediatric patients was 34%. No antibodies that affected efficacy, safety, serum daclizumab levels or any other clinically relevant parameter examined were detected. The data reflect the percentage of patients whose test results were considered positive for antibodies to daclizumab in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to daclizumab with the incidence of antibodies to other products may be misleading.

Post-Marketing Experience

The following adverse reactions have been identified and reported during post-approval use of ZENAPAX (daclizumab). Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Severe acute hypersensitivity reactions including anaphylaxis characterized by hypotension, bronchospasm, wheezing, laryngeal edema, pulmonary edema, cyanosis, hypoxia, respiratory arrest, cardiac arrhythmia, cardiac arrest, peripheral edema, loss of consciousness, fever, rash, urticaria, diaphoresis, pruritus, and/or injection site reactions, as well as cytokine release syndrome, have been reported during post-marketing experience with ZENAPAX (daclizumab) . The relationship between these reactions and the development of antibodies to ZENAPAX (daclizumab) is unknown.