

Duloxetine Effective for Fibromyalgia in Women

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VANCOUVER, B.C. — Duloxetine is a safe and effective treatment for fibromyalgia symptoms in both depressed and nondepressed women, Lesley Arnold, M.D., reported at the annual meeting of the American Psychosomatic Society.

Duloxetine (Cymbalta) is approved for the treatment of both major depression and diabetic neuropathic pain. The drug's

efficacy in treating both pain and depression—which often co-occur in fibromyalgia—is probably due to its dual action as a selective serotonin and norepinephrine reuptake inhibitor, said Dr. Arnold, a psychiatrist who is director of women's health research at the University of Cincinnati.

In one of two 12-week studies funded by Lilly Research Laboratories, a total of 354 adult women who met the American College of Rheumatology's criteria for primary fibromyalgia were randomized to re-

ceive 60 mg of duloxetine once a day (118), 60 mg twice daily (116), or placebo (120).

Significant differences in the Brief Pain Inventory (BPI) average 24-hour pain score and the Fibromyalgia Impact Questionnaire (FIQ) were seen within 1 week in both the 60 mg/day and 120 mg/day duloxetine groups compared with placebo, with no significant difference between the two dosages.

In the low- and high-dose groups, 41% of patients experienced a 50% reduction in

overall pain, compared with 23% of patients on placebo, Dr. Arnold reported.

Significant improvements over placebo were also seen in the FIQ total, pain, fatigue, and restfulness upon awakening scores; in the mean tender point threshold and number of tender points; in the Clinical Global Impression (CGI) and Patient Global Impression of Improvement (PGI) scores; in other BPI subscale measures of pain severity and interference; and in several quality of life and functional measures.

This study replicated several findings from a previously published trial of 207 fibromyalgia patients that included a small number of men. Dr. Arnold presented the findings of both trials together in a poster at the meeting.

In the earlier study, 104 patients (89% women) were randomized to 120 mg/day of duloxetine, and 103 (89% women) to placebo. Duloxetine patients improved significantly more than did placebo-treated patients on the FIQ total score, but not significantly more on the FIQ pain score (Arthritis Rheum. 2004;50:2974-84).

Duloxetine-treated patients also had significant reductions compared with placebo-treated patients in BPI scores for average

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pain severity and interference from pain, number of tender points, and FIQ stiffness, as well as several other fibromyalgia-specific and quality of life measures. The differences were only significant for women, but the number of men was quite small, Dr. Arnold noted.

Major depression was present in approximately 40% of the subjects in the earlier single-dose study and in about one-fourth of the subjects in the two-dose study. In both studies, there were no differences between depressed and nondepressed patients in duloxetine efficacy in alleviating pain and fibromyalgia symptoms, suggesting that these effects are not simply due to an improvement in mood, she noted.

In the first study, duloxetine was significantly more likely than placebo to be associated with side effects including constipation, dry mouth, insomnia, and a small mean increase in heart rate. These were typically mild to moderate in severity. Also in that study, anxiety was reported significantly less often with duloxetine than with placebo.

In the more recent study, nausea, dry mouth, constipation, diarrhea, somnolence, decreased appetite and weight, and a small mean increase in systolic and diastolic blood pressure were among the side effects reported more frequently by duloxetine-treated patients than by those on placebo. These side effects were also generally mild to moderate in severity. In all, the drug was safely administered and well tolerated, Dr. Arnold said. ■

BRIEF SUMMARY OF PROCRT[®] PRESCRIBING INFORMATION FOR THE TREATMENT OF ANEMIA IN CHRONIC RENAL FAILURE PATIENTS NOT ON DIALYSIS

PROCRT[®] Epoetin alfa FOR INJECTION

FOR FULL PRESCRIBING INFORMATION FOR ALL INDICATIONS, REFER TO THE PHYSICIANS' DESK REFERENCE[®]

INDICATIONS AND USAGE

PROCRT[®] is indicated for the treatment of anemia associated with CRF in patients not on dialysis. PROCRT[®] is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hemoglobin less than 10 g/dL.

PROCRT[®] is not intended for patients who require immediate correction of severe anemia. PROCRT[®] may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of PROCRT[®] therapy, and must be closely monitored and controlled during therapy.

PROCRT[®] should be administered under the guidance of a qualified physician (see DOSAGE AND ADMINISTRATION in full Prescribing Information).

CONTRAINDICATIONS

PROCRT[®] is contraindicated in patients with: 1. Uncontrolled hypertension; 2. Known hypersensitivity to mammalian cell-derived products; 3. Known hypersensitivity to Albumin (Human).

WARNINGS

Pediatric Use

The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in premature infants which are sometimes fatal.

Thrombotic Events and Increased Mortality

A randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure) was conducted in which patients were assigned to PROCRT[®] treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%. Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% (221 deaths (35% mortality) compared to 631 patients targeted to remain at a hematocrit of 30% (185 deaths (29% mortality)). The reason for the increased mortality observed in these studies is unknown, however, the incidence of non-fatal myocardial infarctions (3.1% vs 2.3%), vascular access thromboses (39% vs 29%), and all other thrombotic events (22% vs 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

Increased mortality was also observed in a randomized placebo-controlled study of PROCRT[®] in adult patients who did not have CRF who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to PROCRT[®] versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events. While the extent of the population affected is unknown, in patients at risk for thrombosis, the anticipated benefits of PROCRT[®] treatment should be weighed against the potential for increased risks associated with therapy.

In a randomized, prospective trial conducted with another Epoetin alfa product, in 939 women with metastatic carcinoma of the breast who were receiving chemotherapy, patients were assigned to receive either Epoetin alfa or placebo for up to a year, in a weekly schedule, with the primary goal of showing improved survival and improved quality of life in the Epoetin alfa treatment arm. This study utilized a treatment strategy designed to maintain hemoglobin levels of 12 to 14 g/dL (hematocrit 36 to 42%). Increased mortality in the first 4 months after randomization was observed among 469 patients who received the erythropoietin product (41 deaths (8.7% mortality) compared to 470 patients who received placebo (16 deaths (3.4% mortality)). In the first four months of the study, the incidence of fatal thrombotic vascular events (1.1% vs 0.2%) and death attributed to disease progression (6.0% vs 2.8%) were both higher in the group randomized to receive Epoetin alfa as compared to placebo. Based on Kaplan-Meier estimates, the proportion of subjects surviving at 12 months after randomization was lower in the Epoetin alfa group than in the placebo group (70% vs 76%), p = 0.012, log rank. However, also in this study, the monitoring and data collection, reliable comparisons cannot be made concerning the effect of Epoetin alfa on overall time to disease progression, progression-free survival, and overall survival.

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) in association with neutralizing antibodies to native erythropoietin, has been observed in patients treated with recombinant erythropoietins. PRCA has been reported in a limited number of patients exposed to PROCRT[®]. This has been reported predominantly in patients with CRF. Any patient with loss of response to PROCRT[®] should be evaluated for the etiology of loss of effect (see PRECAUTIONS: LACK OR LOSS OF RESPONSE). PROCRT[®] should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to PROCRT[®], native erythropoietin, and any other recombinant erythropoietin administered to the patient. Amgen/Ortho Biotech Products, L.P. should be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, PROCRT[®] should not be administered and such patients should not be switched to another product as anti-erythropoietin antibodies cross-react with other erythropoietins (see ADVERSE REACTIONS).

Albumin (Human)

PROCRT[®] contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Hypertension: Patients with uncontrolled hypertension should not be treated with PROCRT[®]; blood pressure should be controlled adequately before initiation of therapy. Up to 80% of patients with CRF have a history of hypertension. Although there does not appear to be any direct pressor effects of PROCRT[®], blood pressure may rise during PROCRT[®] therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with PROCRT[®].

Special care should be taken to closely monitor and aggressively control blood pressure in patients treated with PROCRT[®]. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by initiation of appropriate measures, the hemoglobin may be reduced by decreasing or withholding the dose of PROCRT[®]. A clinically significant decrease in hemoglobin may not be observed for several weeks.

It is recommended that the dose of PROCRT[®] be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period, because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension. In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the hemoglobin should be managed carefully, not to exceed 12 g/dL (see THROMBOTIC EVENTS).

Seizures: Seizures have occurred in patients with CRF participating in PROCRT[®] clinical trials. In adult patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) as compared with later time points.

Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of PROCRT[®] be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Thrombotic Events: During hemodialysis, patients treated with PROCRT[®] may require increased anticoagulation with heparin to prevent clotting of the artificial kidney (see ADVERSE REACTIONS for more information about thrombotic events).

Other thrombotic events (eg, myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred in clinical trials at an annualized rate of less than 0.04 events per patient year of PROCRT[®] therapy. These trials were conducted in adult patients with CRF (whether on dialysis or not) in whom the target hematocrit was 32% to 40%. However, the risk of thrombotic events, including vascular access thrombosis, was significantly increased in adult patients with ischemic heart disease or congestive heart

failure receiving PROCRT[®] therapy with the goal of reaching a normal hematocrit (42%) as compared to a target hematocrit of 30%. Patients with pre-existing cardiovascular disease should be monitored closely.

PRECAUTIONS

The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur (see CONTRAINDICATIONS). In clinical trials, while transient rashes were occasionally observed concurrently with PROCRT[®] therapy, no serious allergic or anaphylactic reactions were reported (see ADVERSE REACTIONS for more information regarding allergic reactions).

The safety and efficacy of PROCRT[®] therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following PROCRT[®] therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

Blood pressure and hemoglobin should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Hematology: Exacerbation of porphyria has been observed rarely in patients with CRF treated with PROCRT[®]. However, PROCRT[®] has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, PROCRT[®] should be used with caution in patients with known porphyria.

In preclinical studies in dogs and rats, but not in monkeys, PROCRT[®] therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of adult patients on dialysis who were treated with PROCRT[®] for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with PROCRT[®].

Hemoglobin in CRF patients should be measured twice a week until hemoglobin has been stabilized, and measured periodically thereafter.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of PROCRT[®] before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to avoid reaching the suggested target hemoglobin too rapidly, or exceeding the suggested target range (hemoglobin of 10 g/dL to 12 g/dL), the guidelines for dose and frequency of dose adjustments (see DOSAGE AND ADMINISTRATION in full Prescribing Information) should be followed.

For patients who respond to PROCRT[®] with a rapid increase in hemoglobin (eg, more than 1 g/dL in any 2-week period), the dose of PROCRT[®] should be reduced because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension.

The elevated bleeding time characteristic of CRF decreases toward normal after correction of anemia in adult patients treated with PROCRT[®]. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Lack or Loss of Response: If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated: 1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see IRON EVALUATION); 2. Underlying infectious, inflammatory, or malignant processes; 3. Occult blood loss; 4. Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders); 5. Vitamin deficiencies: Folic acid or vitamin B12; 6. Hemolysis; 7. Aluminum intoxication; 8. Osteitis fibrosa cystica; 9. Pure Red Cell Aplasia (PRCA). In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to recombinant erythropoietins.

Iron Evaluation: During PROCRT[®] therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during PROCRT[®] therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by PROCRT[®].

Drug Interactions: No evidence of interaction of PROCRT[®] with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenic potential of PROCRT[®] has not been evaluated. PROCRT[®] does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated IV with PROCRT[®], there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

Pregnancy Category C: PROCRT[®] has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. PROCRT[®] should be used during pregnancy only if potential benefits justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated IV, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. PROCRT[®] has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits from day 6 to 18 of gestation.

Nursing Mothers: Postnatal observations of the live offspring (F1 generation) of female rats treated with PROCRT[®] during gestation and lactation revealed no effect of PROCRT[®] at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no PROCRT[®]-related effects on the F2 generation fetuses.

It is not known whether PROCRT[®] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PROCRT[®] is administered to a nursing woman.

Pediatric Use: See WARNINGS: PEDIATRIC USE.

Pediatric Patients Not Requiring Dialysis: Published literature has reported the use of PROCRT[®] in 133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20 years, treated with 50 to 250 Units/kg SC or IV, QW to TW. Dose-dependent increases in hemoglobin and hematocrit were observed with reductions in transfusion requirements.

Geriatric Use: Among 1051 patients enrolled in the 5 clinical trials of PROCRT[®] for reduction of allogeneic blood transfusions in patients undergoing elective surgery 745 received PROCRT[®] and 306 received placebo. Of the 745 patients who received PROCRT[®], 432 (58%) were aged 65 and over, while 175 (23%) were 75 and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hematocrit (See DOSAGE AND ADMINISTRATION). Insufficient numbers of patients aged 65 or older were enrolled in clinical studies of patients were enrolled in the study using the weekly dosing regimen to determine whether the dosing requirements differ for this subpopulation.

Of the 882 patients enrolled in the 3 studies of chronic renal failure patients on dialysis, 757 received PROCRT[®] and 125 received placebo. Of the 757 patients who received PROCRT[®], 361 (47%) were aged 65 and over, while 100 (13%) were 75 and over. No differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hematocrit (See DOSAGE AND ADMINISTRATION).

Insufficient numbers of patients aged 65 or older were enrolled in clinical studies of PROCRT[®] for the treatment of anemia associated with pre-dialysis chronic renal failure, cancer chemotherapy, and Zidovudine-treatment of HIV infection to determine whether they respond differently from younger subjects.

Laboratory Monitoring: The hemoglobin should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. After any dose adjustment, the hemoglobin should also be determined twice weekly for at least 2 to 6 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values (including blood urea nitrogen [BUN], uric acid, creatinine, phosphorus and potassium) should be monitored regularly. During clinical trials in adult patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some adult patients with CRF not on dialysis treated with PROCRT[®], modest increases in serum uric acid and phosphorus were observed. While changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

Diet: As the hemoglobin increases and patients experience an improved sense of well-being and quality of life, the importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF. In US studies in patients on dialysis, hyperkalemia has occurred at an annualized rate of approximately 0.11 episodes per patient-year of PROCRT[®] therapy, often in association with poor compliance to medication, diet, and/or dialysis.

Renal Function: In adult patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients. In patients with CRF not on dialysis, placebo-controlled studies of progression of renal dysfunction over periods of greater than 1 year have not been completed. In shorter term trials in adult patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in patients treated with PROCRT[®] compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine versus time plots in these patients indicates no significant change in the slope after the initiation of PROCRT[®] therapy.

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PROCRT[®] with the incidence of antibodies to other products may be misleading.

A few cases of PRCA associated with antibodies with neutralizing activity have been reported in patients receiving PROCRT[®] (see WARNINGS: PURE RED CELL APLASIA). These cases were observed in patients treated by either SC or IV routes of administration and occurred predominantly in CRF patients.

Adverse Events Reported in Clinical Trials

PROCRT[®] is generally well-tolerated. The adverse events reported are frequent sequelae of CRF and are not necessarily attributable to PROCRT[®] therapy. In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of patients treated with PROCRT[®] during the blinded phase were:

Percent of Patients Reporting Event: Event followed by Patients Treated With PROCRT[®] (n = 200) first, Placebo-treated Patients (n = 135) second:

Hypertension 24%, 19%; Headache 16%, 12%; Arthralgias 11%, 6%; Nausea 11%, 9%; Edema 9%, 10%; Fatigue 9%, 14%; Diarrhea 9%, 6%; Vomiting 8%, 5%; Chest Pain 7%, 9%; Skin Reaction (Administration Site) 7%, 12%; Asthenia 7%, 12%; Dizziness 7%, 13%; Clotted Access 7%, 2%.

Significant adverse events of concern in patients with CRF treated in double-blind, placebo-controlled trials occurred in the following percent of patients during the blinded phase of the studies:

Seizure 1.1%, 1.1%; CVA/TIA 0.4%, 0.6%; MI 0.4%, 1.1%; Death 0%, 1.7%.

In the US PROCRT[®] studies in adult patients on dialysis (over 567 patients), the incidence (number of events per patient-year) of the most frequently reported adverse events were: hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of PROCRT[®] were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, PROCRT[®] administration was generally well-tolerated, irrespective of the route of administration.

Pediatric CRF Patients: In pediatric patients with CRF on dialysis, the pattern of most adverse events was similar to that found in adults. Additional adverse events reported during the double-blind phase in > 10% of pediatric patients in either treatment group were: abdominal pain, dialysis access complications including access infections and peritonitis in those receiving peritoneal dialysis, fever, upper respiratory infection, cough, pharyngitis, and constipation. The rates are similar between the treatment groups for each event.

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with PROCRT[®]. When data from all patients in the US phase 3 multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any 2-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with PROCRT[®] (150 Units/kg TW) relative to the placebo group.

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with PROCRT[®] in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5% to 10% per patient-year.

Thrombotic Events: In clinical trials where the maintenance hematocrit was 35 ± 3% on PROCRT[®], clotting of the vascular access (A-V shunt) has occurred at an annualized rate of about 0.25 events per patient-year, and other thrombotic events (eg, myocardial infarction, cerebral vascular accident, transient ischemic attack, and pulmonary embolism) occurred at a rate of 0.04 events per patient-year. In a separate study of 1111 untreated dialysis patients, clotting of the vascular access occurred at a rate of 0.50 events per patient-year. However, in CRF patients on hemodialysis who also had clinically evident ischemic heart disease or congestive heart failure, the risk of A-V shunt thrombosis was higher (39% vs 29%, p < 0.001), and myocardial infarctions, vascular ischemic events, and venous thrombosis were increased, in patients targeted to a hematocrit of 42 ± 3% compared to those maintained at 30 ± 3% (see WARNINGS).

In patients treated with commercial PROCRT[®], there have been rare reports of serious or unusual thrombo-embolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins. A causal relationship has not been established.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with PROCRT[®] administration during clinical trials. Skin rashes and urticaria have been observed rarely and when reported have generally been mild and transient in nature.

There have been rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema, or urticaria alone. Most reactions occurred in situations where a causal relationship could not be established. Symptoms recurred with rechallenge in a few instances, suggesting that allergic reactivity may occasionally be associated with PROCRT[®] therapy. If an anaphylactoid reaction occurs, PROCRT[®] should be immediately discontinued and appropriate therapy initiated.

OVERDOSAGE

The maximum amount of PROCRT[®] that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 Units/kg TW for 3 to 4 weeks have been administered to adults without any direct toxic effects of PROCRT[®] itself. Therapy with PROCRT[®] can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, PROCRT[®] may be temporarily withheld until the hemoglobin returns to the suggested target range; PROCRT[®] therapy may then be resumed using a lower dose (see DOSAGE AND ADMINISTRATION in full Prescribing Information). If polycythemia is of concern, phlebotomy may be indicated to decrease the hemoglobin.

ORTHO BIOTECH

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