SYNOPSIS

Name of Sponsor/Company: Janssen-Ortho Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: EPREX*	Volume:	
Name of Active Ingredient: epoetin alfa	Page:	

Protocol Number: CR005908	
Title of Study: A parallel group placebo-controlled study to determine an effective dose regimen for EPREX* (epoetin alfa) sterile solution to reduce transfusion requirements in patients undergoing major elective orthopedic surgery	
Investigators: 19 investigators (Drs. Feagan, Tile, Waddell, Smith, Dow, Johnston, Oliver/O'Farrell, Garnett, Laflamme, Godin, Huk, Sandler, Bond/Turner, Wilson, Whitsitt, Laliberte, Warriner)	
Study centres: 17 study centres	
Publication (reference): In preparation	
Studied period (years): 08-MAY-96 to 04-APR-99	Phase of development: 3B
Objectives: The objective of this study was to determine an effective dose regimen to decrease allogeneic transfusion in subjects undergoing elective orthopedic hip replacement surgery.	
Methodology: This was a double blind, randomized, placebo-controlled, multi-centre study with subjects randomized in a 5:5:3 ratio to receive respectively 4 weekly doses of placebo, 20,000U or 40,000U EPREX* (epoetin alfa) sterile solution, starting 4 weeks prior to surgery.	
Number of patients (planned and analyzed): 216 planned; 214 treated; 201 evaluable for ITT: 78 placebo, 79 20,000U and 44 40,000U.	
Diagnosis and main criteria for inclusion: Male and female subjects 18 years of age or older without major medical conditions scheduled for first time hip replacement surgery, hemoglobin 98-137 g/L, adequate iron stores, must not participate in an autologous blood donation program.	
Test product, dose and mode of administration, batch number: Epoetin alfa supplied in 1 ml vial containing 20,000U/ml in a solution preserved with 0.9% benzyl alcohol and buffered with human serum albumin. For subcutaneous administration. Lot no. R6468.	
Duration of treatment: 4 weeks	
Reference therapy, dose and mode of administration, batch number: Matching placebo containing human serum albumin. For subcutaneous administration. Lot nos. R6828 and R5456.	
Criteria for evaluation: **Efficacy**: Transfusion requirements, hemoglobin, hematocrit, reticulocyte count, iron stores, quality of life, time to discharge. **Safety**: Detection of DVT's, adverse events, physical examination, vital signs, clinical laboratory	

tests.

Statistical methods: Proportion of subjects receiving transfusions was compared using Chi-square test and Bonferroni correction for 2 multiple comparisons: 1) placebo versus 20,000U and 2) placebo versus 40,000U; other efficacy parameters were assessed by analysis of variance with specified contrasts to compare: 1) placebo versus 20,000U and 2) placebo versus 40,000U; adverse events and DVT's were compared among the 3 treatment groups and between placebo and the combined EPREX* (epoetin alfa) groups using Chi-square test or Fisher's exact test as appropriate.

SUMMARY-CONCLUSIONS

EFFICACY RESULTS:

Transfusion requirments: The rate of transfusion was significantly reduced in the EPREX* (epoetin alfa) treated groups compared with placebo. Five of 44 (11.4%) subjects in the 40,000U (p=0.001) and 18 of 79 (22.8%) subjects in the 20,000U (p=0.003) groups were transfused compared with 35 of 78 (44.9%) subjects who received placebo.

Hemoglobin and hematocrit: The hemoglobin concentration increased substantially in both active treatment groups compared to placebo. By the day of surgery, the mean increase was +19.5 g/L in the 40,000U group (p<0.001) and +17.2 g/L in the 20,000U group (p<0.001) compared with +1.2 g/L in the placebo group. A similar response in hematocrit was observed.

Reticulocyte count: Both active treatment groups showed a rapid increase in reticulocyte count with a greater response observed in the 40,000U group. By the day of surgery, the mean increase was +37.0 and +58.8 $x10^9$/L respectively in the 20,000U and 40,000U groups compared with +1.8 $x10^9$/L in the placebo group (p<0.001).

Iron stores: A decrease in serum ferritin from baseline to pre-surgery was observed in both active treatment groups while no change was noted in the placebo group. By the day of discharge, serum ferritin increased in all 3 treatment groups with the greatest increase observed in the placebo group.

Quality of life: Subjects' quality of life declined after the surgery. No signicant differences in quality of life were found among the treatment groups in the SF-36 scales. The decline from baseline to post-operative Day 5 in the energy score (p=0.021) and the total score (p=0.034) of the fatigue questionnaire was significantly less in the 40,000U group compared with placebo.

Time to discharge: No significant differences were noted among the 3 treatment groups.

SAFETY RESULTS:

DVT's: No significant differences were found among the 3 treatment groups with resspect to thromboembolic events. The overall rate of DVT was 6%. One pulmonary embolus was reported in a single subject who received placebo.

Adverse events: Overall 99.1% of subjects reported at least 1 adverse event. Most of the adverse events reported in the study were related to the surgery itself. The most common adverse event was pain (86.0%-91.3%). Marked adverse events occurred in 39.1%-42.7% of subjects. More drug

related adverse events were reported in the active treatment groups (p=0.004 among treatment groups; placebo 9.8%, 20,000U 16.3%, 40,000U 32.6%) with the greatest difference reported in iron metabolism disorders (p<0.001 among treatment groups; placebo 0%, 20,000U 1.2%, 40,000U 13.0%).

Deaths: No subjects died in the study.

Serious Adverse Events: Eleven subjects reported a serious adverse event during the study, 2 were considered related to study medication (proximal DVT's, 1 each in placebo and 20,000U groups). Two additional subjects reported a serious adverse event post hospital discharge, neither was considered to be related to study medication.

Clinical Laboratory Evaluations: No clinically meaningful changes were found.

Vital Signs: No clinically meaningful changes were found.

Physical examination findings: No clinically meaningful changes in abnormal findings were found.

CONCLUSION:

Both 20,000U and 40,000U dose regimens were shown to be safe and highly effective in reducing allogeneic blood transfusion in subjects undergoing elective primary hip surgery who did not predonate autologous blood.

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