Sponsor

Hexal AG

Generic Drug Name

HX575 (Recombinant human erythropoietin)

Trial Indication(s)

Chronic Kidney Disease

Protocol Number

2006-66-INJ-14

Protocol Title

Post-authorization safety study to prospectively monitor the incidence of relevant drug-related adverse events and EPO-related lack of efficacy among CKD subjects receiving HX575 recombinant human erythropoietin alfa i.v.

Clinical Trial Phases

Phase IV

Study Start/End Dates

14 Jul 2008 to 10 Feb 2010

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This study was a multi-center, multinational, prospective, single-arm clinical study with a 6-month treatment period.

Centers

115 centers in 10 countries: Austria (5), Bulgaria (6), France (1), Germany (40), Italy (23), Macedonia (8), Poland (15), Romania (5), Russia (4), Ukraine (8)

Objectives:

Primary Objective:

- To extend the safety database of patients with CKD who receive i.v. HX575 treatment and to monitor the adverse event (AE) profile under post-approval conditions.

Test Product (s), Dose(s), and Mode(s) of Administration

HX575; solution in pre-filled syringe (1000 IU/syringe) was administered intravenously.

Statistical Methods

The statistical analysis was based on the following study populations:

Full analysis set (FAS): all patients who received at least one dose of HX575 after enrollment into this study

Per protocol set (PPS): all patients in the FAS who had no major protocol violation

No statistical hypothesis was tested; only descriptive methods were used to analyze the efficacy and safety endpoints. Analysis of all safety endpoints were conducted using the FAS. Efficacy analyses were based on both, the FAS and the PPS. The incidence of relevant drug-related adverse events and of lack of efficacy events together with exact two-sided 95% confidence intervals was provided based on all patients in the FAS. The number of these events relative to patient years was presented in addition. Interim analyses were neither planned nor performed during the course of the study.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- CKD subjects with or without dialysis treatment.
- Age over 18 years.
- Subjects requiring i.v. erythropoiesis-stimulating agent (ESA) treatment.
- Subjects likely to remain on i.v. ESA treatment for 6 months.
- Provision of informed consent.

Exclusion criteria

- Systemic immunosuppressive medication or any other drugs known to adversely affect the hemoglobin level.
- Known primary lack of efficacy (LOE), unexplained loss of effect to a recombinant erythropoietin product.
- History of PRCA or aplastic anemia.
- History of anti-erythropoietin antibodies.
- Uncontrolled hypertension.
- Pregnant woman or nursing mother.
- Women of childbearing potential do not agree to maintain effective birth control during the study treatment period.

Participant Flow Table

Study populations

Description	Number of patients
Enrolled	1698
Exposed	1695
Full analysis set	1695
Per-protocol set	1143

Baseline Characteristics

Summary of demographic parameters

Parameter	FAS
Age (years)	
Mean	61.8
SD	15.4
Sex	
Male (%)	958 (56.5%)
Female (%)	737 (43.5%)

Summary of Efficacy

Primary Outcome Result:

Refer to Safety Result section for the safety part of the primary outcome result.

Efficacy on hemoglobin value: mean values remained stable between 11.2 and 11.3 g/dl throughout the course of treatment by HX575 IV and transfusion frequency was stable over the course of the study.

Summary of Safety

Safety Results

Incidence of frequent treatment emergent Adverse Effects (TEAEs) (≥ 5% in either treatment group) during the treatment period

	Number of patients (%)
TEAEs	1314 (77.5%)

Most frequently reported TEAEs (in at least 5%) were muscle spasms, headache, hypertension, diarrhea, hypotension, bronchitis, procedural hypotension, nausea, vomiting and nasopharyingitis.

TEAEs suspected to be related to study drug

	Number of patients
Study drug related TEAEs	119 (7%)

The most frequent related TEAE (in at least 1%) were hypertension and headache.

Serious Adverse Events and Deaths

Description	Number of patients (%)
Serious TEAE*	456 (26.9%)
Serious TEAE treatment-related	11 (0.6%)
Deaths (During treatment period)	82(4%)
Deaths (After treatment period)	11 (0.6%)
Discontinuation	30 (5.5%)

Among serious TEAEs, treatment-related, there were 2 cases of anemia, including a fatal one. Overall 3 patients (0.18%) were suspected to have ESA-related lack of efficacy and all required a transfusion for the event. In one of them a clinically suspected PRCA was suspected but no anti-EPO antibodies detected and the case was considered not EPO related by the Drug Safety Monitoring Board. All samples tested for anti-Epo antibodies were negative

Other Relevant Findings

Not Applicable

Date of Clinical Trial Report

26 Oct 2010