Anemia therapy in patients with chronic kidney disease: Role of epoetin zeta

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Renal Anemia

- A severe complication of chronic kidney disease (CKD)
- Seen in more than 80% of CKD patients
- Inadequate production of erythropoietin by damaged kidneys
- Correction by erythropoiesis stimulating agents (ESAs)
- Adjuvant therapy (e.g. intravenous iron) for optimal ESA response
Treatment of renal anemia with erythropoiesis stimulating agents

- Epoetin alfa
- Epoetin beta
- Darbepoetin alfa
- C.E.R.A.
- Biosimilars
- Hematide
Epoetin Zeta

- New recombinant human erythropoietin
- Identical to epoetin alfa in its amino acid sequence
- Comparable in its carbohydrate composition
- Classified as biosimilar to epoetin alfa
Comparison of the galenics between epoetin zeta, epoetin beta, and epoetin alfa

<table>
<thead>
<tr>
<th>Epoetin zeta</th>
<th>Epoetin beta</th>
<th>Epoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate 20</td>
<td>Polysorbate 20</td>
<td>Polysorbate 80</td>
</tr>
<tr>
<td>Sodiumdihydrogenphosphate</td>
<td>Sodiumdihydrogenphosphate</td>
<td>Sodiumdihydrogenphosphate</td>
</tr>
<tr>
<td>Sodiummonohydrogenphosphate</td>
<td>Sodiummonohydrogenphosphate</td>
<td>Sodiummonohydrogenphosphate</td>
</tr>
<tr>
<td>Calciumchloride</td>
<td>Calciumchloride</td>
<td>Calciumchloride</td>
</tr>
<tr>
<td>Glycine</td>
<td>Glycine</td>
<td>Glycine</td>
</tr>
<tr>
<td>Leucine</td>
<td>Leucine</td>
<td>Leucine</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Isoleucine</td>
<td>Isoleucine</td>
</tr>
<tr>
<td>Threonine</td>
<td>Threonine</td>
<td>Threonine</td>
</tr>
<tr>
<td>Glutamine acid</td>
<td>Glutamine acid</td>
<td>Glutamine acid</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Phenylalanine</td>
<td>Phenylalanine</td>
</tr>
<tr>
<td>Sodiumchloride</td>
<td>Sodiumchloride</td>
<td>Sodiumchloride</td>
</tr>
<tr>
<td>Sodium monohydrogenphosphate</td>
<td>Sodium monohydrogenphosphate</td>
<td>Sodium monohydrogenphosphate</td>
</tr>
<tr>
<td>Urea</td>
<td>Urea</td>
<td>Urea</td>
</tr>
<tr>
<td>Water for injection</td>
<td>Water for injection</td>
<td>Water for injection</td>
</tr>
</tbody>
</table>

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Biosimilars

- Biological products
- Closely related (similar) to the reference product
- Not necessarily identical
- Therapeutic equivalence to the reference product
  - Efficacy
  - Safety
  - Tolerability
- Erythropoietin-specific biosimilar guidelines by the European Medicines Agency (EMEA)
Iso-electro-focus gel with western blots for isoform detection: (A) samples from China (lanes 2-9) and Korea (lanes 10-13) and (B) samples from India (lanes 1-5)

Results of quality by design approach: Binocrit® equivalence demonstrated with physicochemical analysis

Physicochemical analysis techniques allow high resolution comparison of new and existing versions of medicines.

Gel electrophoresis technique is a useful starting point for comparison.

Other more modern techniques allow comparison at the atomic level.
Anti-EPO antibody-mediated pure red cell anemia (PRCA)

- Progressive, severe, transfusion-dependent anemia (with sudden onset)
- Decline of hemoglobin levels by 1 g/dl per day
- Low reticulocyte counts
- Decreased number of bone marrow erythroid precursors
- ESA- and iron-resistant anemia
- Detection of neutralizing anti-erythropoietin antibodies against exogenous and endogenous erythropoietin

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Potential risk factors for immunogenicity of erythropoiesis stimulating agents (1)

- Subcutaneous injection
- Interruption of cooling
- Protein degradation (during production and/or storage)
- Protein modification (e.g. oxidation of Met-54 or Trp-64)
- Protein denaturation (alterations of protein structure)
- Formation of dimers and aggregates
- „Microparticles“
Potential risk factors for immunogenicity of erythropoiesis stimulating agents (2)

- Organic softeners
- Silicon oil
- Metal ions (tungsten)
- Polysorbate micelles
- Host cell proteins (HCP)
- Specific interactions between the product (epoetin) and the patients (HLA system)
Anemia therapy in patients with chronic kidney disease: Role of epoetin zeta

Four important studies for the efficacy, safety and tolerability


Baseline demographic and clinical data of the safety population (n = 609)


Total number of patients screened (visit 1, entry)  
\[ n = 780 \]

Total number of patients randomized (safety population)  
\[ n = 609 \]

Patients excluded  
\[ n = 171 \]
- exclusion criterion met, \[ n = 161 \];
- adverse event, \[ n = 6 \];
- withdrawal of patient consent, \[ n = 2 \];
- contact with patient lost, \[ n = 2 \]

Epoetin zeta  
\[ n = 305 \]

Epoetin alfa  
\[ n = 304 \]

Patients treated less than 1 month with study medication  
\[ n = 5 \]

Patients treated less than 1 month with study medication  
\[ n = 6 \]

Full analysis set  
\[ n = 300 \]

Full analysis set  
\[ n = 298 \]

Excluded from per-protocol set  
\[ n = 27 \]

Excluded from per-protocol set  
\[ n = 30 \]

Per-protocol set  
\[ n = 273 \]

Per-protocol set  
\[ n = 268 \]
Comparison of the therapeutic effects of epoetin zeta and epoetin alfa in the correction of renal anemia


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Proportion of patients with (cumulative) treatment success

Long-term safety and tolerability of epoetin zeta, administered intravenously, for maintenance treatment of renal anemia (1)


Long-term safety follow-up trial
\( n=745 \)

Preceding maintenance treatment trial
\( n=232 \)
- Germany
  \( n=176 \)
- Poland
  \( n=56 \)

Preceding dose-titration trial
\( n=513 \)
- Bulgaria
  \( n=231 \)
- Poland
  \( n=105 \)
- Serbia
  \( n=177 \)
Long-term safety and tolerability of epoetin zeta, administered intravenously, for maintenance treatment of renal anemia (2)

Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anemia treatment (1)

Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anemia treatment (2)

Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anemia treatment (3)


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Disposition of hemodialysis patients for the SC epoetin zeta study


Total number of patients screened (visit 1)
\( n = 707 \)

Total number of patients randomized (safety population)
\( n = 462 \)

**Epoetin zeta**
\( n = 232 \)

- Patients treated less than 4 weeks with randomized study medications
  \( n = 4 \)

- Full analysis set
  \( n = 228 \)

- Major protocol violations
  \( n = 74 \)

- Per-protocol set
  \( n = 154 \)

**Epoetin alfa**
\( n = 230 \)

- Patients treated less than 4 weeks with randomized study medications
  \( n = 8 \)

- Full analysis set
  \( n = 222 \)

- Major protocol violations
  \( n = 57 \)

- Per-protocol set
  \( n = 165 \)

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Baseline demographic and clinical characteristics, safety population (n=462) (1)


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Epoetin zeta (n=232)</th>
<th>Epoetin alfa (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>94 (40.5)</td>
<td>96 (41.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>138 (59.5)</td>
<td>134 (58.3)</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>55.6 ±12.47</td>
<td>55.2 ± 12.58</td>
</tr>
<tr>
<td>Height, cm (mean ± SD)</td>
<td>167.9 ± 8.77</td>
<td>167.0 ± 9.50</td>
</tr>
<tr>
<td>Weight, kg (mean ± SD)</td>
<td>70.5 ± 15.11</td>
<td>70.8 ± 15.84</td>
</tr>
<tr>
<td>Time since end-stage renal failure, months (median)</td>
<td>37.0</td>
<td>36.5</td>
</tr>
<tr>
<td>Diagnosis leading to renal failure, n=+%:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>31 (13.4)</td>
<td>25 (10.9)</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>36 (15.5)</td>
<td>34 (14.8)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>73 (31.5)</td>
<td>69 (30.0)</td>
</tr>
<tr>
<td>Other</td>
<td>92 (39.7)</td>
<td>102 (44.3)</td>
</tr>
</tbody>
</table>

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### Baseline demographic and clinical characteristics, safety population (n=462) (2)

**Krivoshiev S et al, Adv Ther 27: 105-117, 2010**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Epoetin zeta (n=232)</th>
<th>Epoetin alfa (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dL (mean ± SD*)</td>
<td>10.56 ± 1.35</td>
<td>10.40 ± 1.43</td>
</tr>
<tr>
<td>Hematocrit, % (mean ± SD*)</td>
<td>31.9 ± 4.4</td>
<td>31.3 ± 4.1</td>
</tr>
<tr>
<td>Heart rate, beats/min (mean ± SD)</td>
<td>76.2 ± 9.59</td>
<td>74.7 ± 8.48</td>
</tr>
<tr>
<td>Blood pressure, systolic, mmHg (mean ± SD)</td>
<td>135.6 ± 17.81</td>
<td>136.7 ± 16.99</td>
</tr>
<tr>
<td>Blood pressure, diastolic, mmHg (mean ± SD)</td>
<td>78.5 ± 10.30</td>
<td>79.5 ± 9.59</td>
</tr>
</tbody>
</table>

* Values for the per-protocol set
Mean Hb level during the last 4 weeks of treatment with epoetin zeta versus epoetin alfa in hemodialysis patients

Mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment with epoetin zeta versus epoetin alfa

Selected major serious adverse events, safety population (n=462)


<table>
<thead>
<tr>
<th>Serious adverse events</th>
<th>Epoetin zeta (n=232)</th>
<th>Epoetin alfa (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension/hypertensive crisis, %</td>
<td>3.3</td>
<td>5.9</td>
</tr>
<tr>
<td>Thrombotic vascular events, %</td>
<td>4.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Hemorrhagic/ischemic stroke, %</td>
<td>4.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>2.2</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Possible reasons for ESA hyporesponse in patients with chronic kidney disease

- **Traditional risk factors**
  - Iron-, vitamin-, folic acid deficiency
  - Infect/Inflammation
  - Malignom
  - Hematologic disease

- **Non-traditional risk factors**
  - Secondary hyperparathyroidism
  - Hypervolemia/congestive heart failure
  - Dialysis catheters/synthetic grafts
  - Non-sterile dialysate
  - Failed kidney graft
  - Uremic toxins/underdialysis

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Hemoglobin (Hb) level or change from baseline for trials comparing intravenous (IV) iron versus oral iron in dialysis patients

Estimated proportion of 1774 hemodialysis patients from New York surviving by levels of IV iron administration

Pollak VE et al, BMC Nephrol 10: 6, 2009
Estimated proportion of 1774 hemodialysis patients from New York surviving by four levels of TSAT

Pollak VE et al, BMC Nephrol 10: 6, 2009
Estimated proportion of 1774 hemodialysis patients from New York surviving by five levels of serum ferritin

Pollak VE et al, BMC Nephrol 10: 6, 2009

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Multivariate adjusted association between serum ferritin and all-cause mortality: Quarterly serum ferritin and 2-year survival in 58,058 MHD patients


<table>
<thead>
<tr>
<th>Ferritin (ng/mL)</th>
<th>New K/DOQI range: &gt;200 ng/mL</th>
<th>Old K/DOQI: up to 800 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-99</td>
<td></td>
<td></td>
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<tr>
<td>100-199</td>
<td></td>
<td></td>
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<tr>
<td>200-299</td>
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<tr>
<td>300-499</td>
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<tr>
<td>500-649</td>
<td></td>
<td></td>
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<tr>
<td>650-799</td>
<td></td>
<td></td>
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<tr>
<td>800-999</td>
<td></td>
<td></td>
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<tr>
<td>1000-1199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1200-1499</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1500-1999</td>
<td></td>
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<tr>
<td>&gt;= 2000</td>
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</tbody>
</table>

All cause death hazard ratio

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Relationship between EPO/Hct and albumin, CRP, and ferritin levels in PD patients

Changes in individual data in both groups for (A) Hb levels, (B) TSATs, and (C) CRP levels

Association between (1) the mean monthly percentage change in EPO dose and the risk of death and (2) the month-6 achieved Hb level and the risk of death.

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Adjusted hazard ratios and 95% confidence intervals from multivariable Cox regression including an interaction of ESA use and hemoglobin level


<table>
<thead>
<tr>
<th>Hemoglobin level</th>
<th>(A) ESA non-users</th>
<th>(B) ESA users</th>
<th>(C) ESA users vs. non-users</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.5 g/dl</td>
<td>3.5 (2.0 to 6.0)</td>
<td>8.0 (3.1 to 20.6)</td>
<td>1.4 (0.9 to 1.9)</td>
</tr>
<tr>
<td>11 g/dl</td>
<td>2.5 (1.5 to 4.0)</td>
<td>4.7 (2.1 to 10.5)</td>
<td>1.1 (0.7 to 1.7)</td>
</tr>
<tr>
<td>12.5 g/dl</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>0.6 (0.2 to 1.5)</td>
</tr>
<tr>
<td>14 g/dl</td>
<td>0.7 (0.4 to 1.5)</td>
<td>2.8 (1.0 to 7.9)</td>
<td>2.2 (0.8 to 6.0)</td>
</tr>
<tr>
<td>15.5 g/dl</td>
<td>0.7 (0.3 to 1.6)</td>
<td>4.7 (1.4 to 16.2)</td>
<td>3.8 (1.3 to 10.9)</td>
</tr>
</tbody>
</table>
Potential advantages with the use of epoetin zeta for the treatment of renal anemia

- Biosimilar which can safely be administered subcutaneously in CKD patients
- Biosimilar without any case of pure red cell aplasia (so far)
- Biosimilar with therapeutic equivalence to the reference product
- Biosimilar with long-term efficacy, safety and tolerability data
- Biosimilar which probably reduces costs for anemia therapy
Anemia therapy in patients with chronic kidney disease: Role of epoetin zeta

Summary (1)

- Renal anemia a frequent and severe complication in CKD patients
- Correction of renal anemia (target hemoglobin levels 10-12 g/dl) by ESAs and adjuvant therapies (e.g. iron)
- Biosimilar epoetin zeta a novel ESA for anemia therapy
Anemia therapy in patients with chronic kidney disease: Role of epoetin zeta

Summary (2)

- Long-term safety, tolerability and efficacy data
  - Therapeutically equivalent to epoetin alfa in the correction of low hemoglobin concentration (by the IV route of administration)
  - Effective regarding its ability to maintain stabilized hemoglobin levels within the target range (by the IV route of administration)
  - Therapeutically equivalent to the reference product in respect to efficacy, safety and tolerability (even if administered subcutaneously)
End