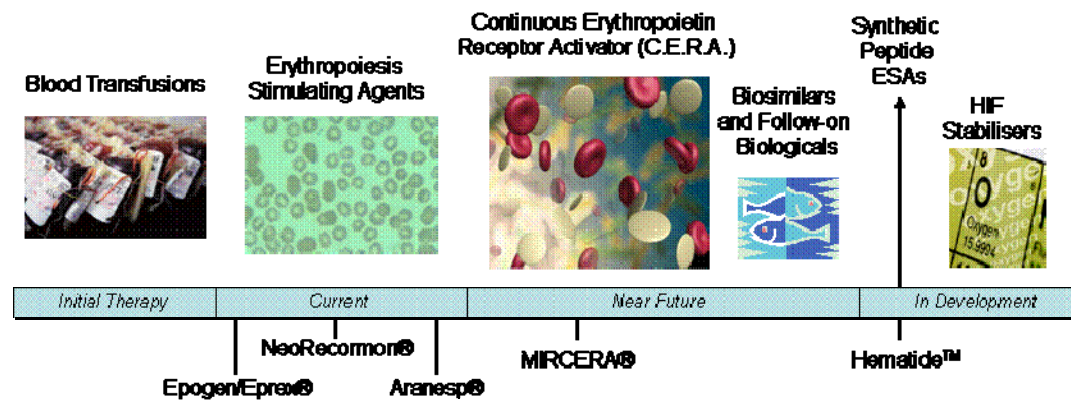


## Anaemia Treatment: Past, Present, Future

### Introduction

The treatment for anaemia associated with chronic kidney disease (CKD) is now an established part of patient care. Prior to the late 1980's blood transfusion was the only treatment option available<sup>i</sup>. Now, drugs which stimulate the erythropoietic process are the mainstay of therapy as they have shown to slow down the inevitable deterioration of cardiac function associated with severe anaemia (Hb < 11 g/dL)<sup>ii</sup>. An overview of the first of these drugs called erythropoiesis stimulating agents (ESAs) is given below, as are details of the first in the new class of agents called C.E.R.A, which is poised to provide the next important step in improving care and outcomes for patients with CKD and anaemia.

Diagram to show the development of treatments for anaemia associated with CKD:



### Blood Transfusion

Originally blood transfusions for patients with renal anaemia were needed every 2-3 weeks<sup>iii</sup>. With the availability of ESAs, blood transfusions are generally reserved for immediate correction of low haemoglobin levels in patients suffering from a bleeding event. With a decreased dependence on blood transfusions, not only is the burden on the blood banks reduced but also the risks associated with blood transfusion, for example, exposure of patients to transmissible infections<sup>iv</sup>. Additionally, blood products place a large cost

burden on health services, with increasing demands on blood stocks having a corresponding increase in cost. Costs of blood transfusions include not only the direct costs of the product but also the indirect costs of associated hospital care, medical staff costs and patient and societal costs<sup>v</sup>. Furthermore, blood transfusions result in haemoglobin levels that are highly unstable and represent a volume stress on otherwise fragile patients, therefore alternative treatments should be considered.

### **Erythropoietic Stimulating Agents (ESAs)**

The breakthrough in research for treatments to stimulate erythropoiesis occurred in 1977 with the purification of human erythropoietin<sup>vi</sup>. Gene cloning and molecular biology techniques then allowed for the mass production of ESAs<sup>vii,viii</sup>. ESAs approved for the treatment of renal anaemia are outlined below (see table 1 for summary).

Epogen<sup>®</sup>/Eprex<sup>®</sup>/Procrit<sup>®</sup> (epoetin alfa) was the first ESA approved for the treatment of anaemia associated with CKD in 1989<sup>ix</sup>. Epoetin alfa is administered by either subcutaneous or intravenous injection, but as it is short-acting, must be dosed two to three times a week to maintain adequate haemoglobin levels (Hb). Once-weekly dosing regimens have been studied essentially in patients not on dialysis, but the product's short half life has required frequent dose adjustments and has limited the proportion of patients able to tolerate the longer interval between doses<sup>x,xi</sup>. An upsurge of a rare but life-threatening condition known as pure red cell aplasia or Anti Erythropoietin antibody mediated PRCA (a sudden and sharp decrease in red blood cell production) has been associated with the use of Eprex<sup>®</sup>. A change in the formulation of the product in 1998 is thought to have affected the stability of the compound, which provoked an immune response underlying PRCA in these patients<sup>xii</sup>.

NeoRecormon<sup>®</sup> (epoetin beta) which was approved in 1990 has a different molecular structure than epoetin alfa. The altered structure gives epoetin beta a longer elimination half-life<sup>xiii</sup>. Epoetin beta, which is sold in over 150 countries in Europe and Asia, has been shown to be effective and well tolerated when administered both subcutaneously and intravenously. Haemoglobin correction is achieved with dosing schedules of up to 3 times a week. Hb levels can then be maintained reliably with a convenient once-weekly dosing schedule or once every two weeks<sup>xiv,xv,xvi</sup>. Once-weekly epoetin beta given subcutaneously has been shown to significantly reduce the amount of medicine that patients need when compared to darbepoetin alfa iv/sc and epoetin beta iv (a 30% dose saving has been shown). This is likely to provide cost savings to health services<sup>xvii</sup>. Subcutaneous epoetin beta is associated with less pain on injection than subcutaneous darbepoetin alfa<sup>xviii</sup>.

**Aranesp® (darbepoetin alfa)**, was approved for use in 2001. Darbepoetin alfa is larger and heavier than epoetin alfa and epoetin beta (additional sugar molecules have been added to its structure) giving it an increased elimination half life of 33-48 hours<sup>xix,xx</sup>. Darbepoetin alfa is used in the maintenance setting once-weekly in CKD patients on dialysis and once every two weeks in CKD patients not on dialysis<sup>xxi,xxii</sup>. Subcutaneous darbepoetin alfa once every four weeks is also approved by the EMEA for maintenance of haemoglobin in a sub-group of patients not on dialysis who have demonstrated stability on a once every two week regimen of darbepoetin alfa. A monthly regimen has also been approved in Switzerland.

**Dynepo® (epoetin delta)**, is an erythropoietin produced in a human cell line<sup>xxiii,xxiv</sup>. Although approved in the EU in 2002, it has not yet launched.

**Table 1.**

The table below summarises the range of currently approved ESA's for renal anaemia.

| ESA              | Approval status   |  | Frequency of dosing   |
|------------------|---|--|---|
|                  | U.S.  | Europe   |   |
| Epoetin alfa     | Epogen® (Amgen) – Dialysis patients only, Procrit® (Ortho Biotech) – Pre-dialysis patients only | Eprex® (Janssen-Cilag)   | 1-3 times weekly iv and sc  |
| Epoetin beta     | Not approved for use in the U.S.  | NeoRecormon® (Hoffmann-La Roche)                                       | 3 times weekly iv and sc. After anaemia is corrected, haemoglobin levels can be maintained with a once-weekly dose in sc. A once every two-week dose is also approved in maintenance.   |
| Epoetin delta    | Not approved for use in the U.S.  | Dynepo® (Shire, approved but not yet available – expected launch 2007) | 3 times weekly for intravenous administration, 2 times weekly for subcutaneous administration.  |
| Darbepoetin alfa | Aranesp® (Amgen)  | Aranesp® (Amgen) Nespo® (Dompe Biotech, SPA)                           | Once weekly. After anaemia is corrected, haemoglobin levels can be maintained with 1 dose every 2 weeks. Approved for once-monthly dosing in Switzerland in dialysis patients. Approved for once-monthly dosing in Europe in pre-dialysis patients (who have demonstrated Hb stability after correcting with once every other week dosing). |

### Biosimilars and Follow-on Biologicals

Biosimilars (term used outside US) and Follow-on-Biologicals (term used in US) are follow-on products to

biological medicines that have reached patent expiry. They are produced with the aim of having similar properties than the original product. Since the production of biotechnology products is complex, even subtle differences in manufacturing will result in differences in the properties of the biosimilar when compared to the original. These differences may impact patient safety, therefore it is important that any biosimilar experiences robust clinical testing in addition to extensive technical and preclinical testing. The European Medicines Agency (EMA) recently published product specific guidelines defining the minimal phase III clinical program required to ascertain enough similarity to the original product<sup>xxv</sup> and requesting a risk management/pharmacovigilance plan as well as long-term monitoring of immunogenicity. It is expected that the first biosimilars of epoetin alfa may be launched in Europe in 2007.

### **The needs of future therapy**

Although ESAs have been invaluable in effective anaemia management, considerable variability in haemoglobin levels occurs during therapy with clinical and economic consequences.

- Over 60 % of CKD patients have Hb levels outside the recommended target range at any one time<sup>xxvi</sup>.
- The highest rates of hospitalization and mortality are seen in patients in whom haemoglobin levels remain below the target range<sup>xxvii</sup>.
- Correction of Hb levels above the maximum target range may result in unnecessary drug use and associated costs<sup>xxviii</sup>.

Therefore, the development of improved therapies which have the potential to advance haemoglobin control and improve patient outcomes has continued.

### **The C.E.R.A. Class**

MIRCERA® is the first of a new class that of agents called C.E.R.A. (Continuous Erythropoietin Receptor Activator) and represents significant progress in anaemia management. MIRCERA is a new complex chemical entity with the longest half life of any agent to date - 134 hours with intravenous use and 139 hours with subcutaneous use<sup>xxix,xxx</sup>. Unlike the first short-acting ESAs, MIRCERA has a greatly reduced affinity for erythropoietic receptors, allowing it to stimulate red cell production without immediate internalization and degradation. This distinct molecular interaction is believed to play a role in providing targeted, stable and sustained control of anaemia.

### **Correction**

- Studies show that for previously untreated renal anaemia patients, MIRCERA achieves a 93 – 97.5% response rate in correcting Hb with twice-monthly dosing<sup>xxxi</sup>. If approved; MIRCERA would be the first

drug to correct anaemia in patients with CKD on dialysis and not on dialysis using a twice-monthly dosing schedule<sup>xxxii,xxxiii</sup>.

### Maintenance

- For patients with CKD on dialysis, once monthly maintenance therapy with MIRCERA either intravenous or subcutaneous provides long-term tight control of Hb within the target range, as recommended in international guidelines. This result is achieved in patients converting directly from epoetin 1-3x/wk and is maintained over the long term. By maintaining Hb within a narrow target range, once-monthly MIRCERA has the potential to optimize anaemia management, allowing physicians more time to manage other complications of CKD<sup>xxxiv</sup>.

### HIF stabilisers and synthetic peptide ESAs

Synthetic peptide ESAs, are manufactured amino acid sequences (building blocks of proteins) which, although they are not structurally related to erythropoietin, aim to mimic its effects<sup>xxxv</sup>. *In-vitro* and *in-vivo* studies have shown one such agent, Hematide<sup>TM</sup>, to have erythropoietic effect, long half life and slow clearance time<sup>xxxvi,xxxvii</sup>. It is currently in phase II of its clinical trial programme<sup>xxxviii</sup>.

In even earlier stages of development are the HIF stabilisers. Hypoxia inducible factor (HIF) becomes active when circulating oxygen levels fall. HIF is involved in regulating a very large number of metabolic pathways including the erythropoietic process. HIF stabilisers influence this by inhibiting the natural degradation of HIF in the body which helps to prolong erythropoiesis. HIF stabilisers can be dosed orally<sup>xxxix</sup>.

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