Epogen® Mechanism of Action

(Four 2-3 minute animations)

1. PATHOPHYSIOLOGY OF ANEMIA IN PATIENTS WITH CHRONIC RENAL FAILURE (CRF)

In the body, the rate of red blood cell production is kept in balance by a feedback loop which includes the kidneys, the bone marrow and the bloodstream. **[Guyton Textbook of Medical Physiology. 11th ed. 2006:422, fig. 32-4; 423, A,3]** Red blood cells contain an oxygen carrying protein called hemoglobin and have the critical function of supplying oxygen to the body's tissues. **[Guyton Textbook of Medical Physiology. 11th ed. 2006:424, A,4; B,2; 425, A,1; Hillman Red Cell Manual. 7th ed. 1996: 12, A,1]** Kidney cells within the renal cortex and outer medulla are sensitive to blood oxygen levels. In healthy individuals, these kidney cells respond to hypoxia—low oxygen levels in the blood—by producing and releasing a hormone called erythropoietin. **[Guyton AC. Textbook of Medical Physiology. 11th ed. 2006:422, B,2,3; 423, A,2-4; Hillman. Red Cell Manual. 7th ed. 1996: 6, A,2]** Erythropoietin then circulates to the bone marrow and stimulates red blood cell production and development. **[Guyton, AC. Textbook of Medical Physiology. 11th ed. 2006: 422, B,2 and fig 32.4; Hillman, Red Cell Manual. 7th ed. 1996: 4, A,1; Papayannopoulou, et al. Hematology: Basic Principles and Practice. 4th ed. 2005 pg 272, A,4]** The consequent increase in red blood cells eliminates the hypoxic stimulus and decreases erythropoietin production by the kidneys—closing the feedback loop. Therefore, it can be said that RBC production is controlled by a feedback loop regulated by tissue oxygen levels. **[Guyton, AC. Textbook of Medical Physiology. 11th ed. 2006: 422, B,2 and figure 32.4; 423, A,3; Tilley B. *Nephrol Nurs J.* 2004;31: 75,A,3–75,B,1]**

In dialysis patients with chronic renal failure, the normal feedback loop is often compromised. Due to the kidneys' declining function, even in a state of hypoxia, they are unable to produce sufficient amounts of erythropoietin. **[Guyton AC. Textbook of Medical Physiology. 11th ed. 2006:423, A, 2 and4; Besarab A. Diseases of the Kidney. 8th ed. 2007:chap 92. 18, A,2;]** The insufficient level of erythropoietin leads to decreased production of red blood cells. Thus, in these patients, inadequate erythropoietin is the primary cause of anemia. **[Guyton AC. Textbook of Medical Physiology. 11th ed. 2006:423, A,2,4; Eschbach, *Nephrol Dial Transplant.* 2002;17(suppl 5):6, A,1; Tilley B. Nephrol Nurs J. 2004;31:75,B1]**

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2. ERYTHROKINETICS

Erythrokinetics refers to the production, accumulation, and destruction of red blood cells, or RBCs. **[Chmielewski CM. *ANNA J.* 1995;22:420, B,1,3; 421, A,1,2; Uehlinger DE, et al. *Clin Pharmacol Ther.* 1992;51:76, B,1]**

In normal physiology, there is a steady state of production and destruction of red blood cells, which have a typical lifespan of 120 days. **[Hillman Red Cell Manual. 7th ed. 1996: 12, A,1; Breiterman-White. Nephrol Nurs J. 2008;35:577, B,3, C,1; Hutson PR. In: Lee M, ed. *Basic Skills in Interpreting Laboratory Data.* 2004:chap 15. 444, A,3]** Barriers to the production of red blood cells or the acceleration of their death can cause anemia. **[Besarab A. Diseases of the Kidney. 8th ed. 2007: chap 92.18,A,2;]**

Patients with chronic renal failure who are on dialysis frequently have inadequate erythropoietin production which results in decreased RBC production. **[Guyton AC. Textbook of Medical Physiology. 11th ed. 2006:423, A, 2 and4; Besarab A. Diseases of the Kidney. 8th ed. 2007:chap 92. 18, A,2]**The RBCs produced in these patients have a lifespan of about 64 days, about one half of the lifespan of red blood cells in a healthy person. **[Chmielewski CM. *ANNA J.* 1995;22: 421,B,3; C,2; Breiterman-White. *Nephrol Nurs J.* 2008;35:577, C,1]**

The erythrokinetic dynamic is altered when therapy with EPOGEN® (Epoetin alfa) is initiated. The RBC production rate begins to increase until RBC production outpaces RBC cell death. **[Chmielewski CM. *ANNA J.* 1995;22: 421,C,2 and Fig. 2; Uehlinger DE, et al. *Clin Pharmacol Ther.* 1992;51:77, A,1, 2; 78, Fig 1; Sargent JA, et al. *Blood Purif.* 2004;22: 112,B,2; 113,A,1,2 and fig 1]** This will result in an increase in hemoglobin until the production rate and death rate of RBCs becomes equal. **[EPOGEN® PI, 4/09 v21:2,A,6; 17, A,7; Sargent JA, et al. *Blood Purif.* 2004;22: 112,B,2; 113,A,1 and fig 1; Chmielewski CM. *ANNA J.* 1995;22: 420, B,1,3; 421, A,tbl 2; 421, A,2, B,2,3]**

An increased production rate of RBCs, requires availability of adequate iron levels. Once erythropoiesis is initiated with EPOGEN®, iron should be an adjuvant treatment. **[Beleslin-Cokic BB, et al. *Blood.* 2004;104: 2073,A,1; EPOGEN® PI, 4/09 v21: 15, A, 7,8; 27,A,6; Stivelman JC. *Dialysis Therapy.* 3rd ed. 2002: 326,A,3, B,1]**

Discontinuation of EPOGEN® therapy will initially result in a state wherein RBC death outpaces RBC production, decreasing hemoglobin levels. These levels will decrease until a lower steady state is achieved. This lower steady state will persist until therapy is resumed. **[EPOGEN® PI, 4/09 v21: 2,A,6; 17, A,7; Sargent JA, et al. *Blood Purif.* 2004;22: 113, A,fig 1; Chmielewski. CM. *ANNA J.* 1995; 422, B,1 and Fig 3]**

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3. THE ROLE OF IRON AND IMPACT OF IRON DEFICIENCY

Although it is not a stimulant of red blood cell production, iron is a substrate that supports erythropoiesis once cells have been stimulated by erythropoietin. **[Guyton AC. Textbook of Medical Physiology. 11th ed. 2006: 425, A,3; 424, A,4;]** In normal physiology, erythropoietin stimulates the formation of red blood cells – or RBCs. **[Guyton, AC. Textbook of Medical Physiology. 11th ed. 2006: 422, B,2 and fig 32.4; Hillman, Red Cell Manual. 7th ed. 1996: 4, A,1; Papayannopoulou, et al. Hematology: Basic Principles and Practice. 4th ed. 2005 pg 272, A,5]** During the later stages of the RBC maturation process, iron becomes essential. **[Hillman. Red Cell Manual. 7th ed. 1996: 7, A,2; 8, A,3 and Fig. 6; Guyton, AC. Textbook of Medical Physiology. 11th ed. 2006: 425, A,3; Beleslin-Cokic BB, et al. *Blood.* 2004;104:2073,A,1]** Iron can be found within the bloodstream bound to a carrier protein called transferrin. Transferrin receptors are found in abundance on RBC precursors, called erythroblasts. Transferrin binds with these receptors to transport iron into erythroblasts for proper hemoglobin synthesis. **[Hillman. Red Cell Manual. 7th ed. 1996: 8, A,3; 9, A,1; Hutson PR. In: Lee M, ed. *Basic Skills in Interpreting Laboratory Data*. 2004:chap 15. 454, A,1,2; Beleslin-**

Cokic BB, et al. *Blood.* 2004;104:2073,A,1;] After synthesis, iron binds to the hemoglobin molecule, creating a functional oxygen-transporting protein. Once the RBCs are mature, they can then carry oxygen from the lungs to the body's tissues. **[Guyton AC. Textbook of Medical Physiology. 11th ed. 2006: 419, A,2; 424, A,1,4]**

Once the RBCs reach the end of their lifespan, they are engulfed by macrophages in the cells of the reticuloendothelial system, or RES. There, the iron is extracted from hemoglobin and released back into the bloodstream where it can be circulated to the erythroblasts in the bone marrow or stored in the liver as ferritin or hemosiderin. In this way, iron is circulated and reused. **[Lee GR, et al. Wintrobe's Clinical Hematology. 10th ed. 1999: 246,B,5; 247,A,fig 11.9; 249,B,4; Hutson PR. In: Lee M, ed. *Basic Skills in Interpreting Laboratory Data*. 2004:chap 15. 444, A,3]**

In patients with chronic renal failure who are on dialysis, there can be interruptions to this iron recirculation cycle which can result in absolute or functional iron deficiency. **[Wish JB. *Clin J Am Soc Nephrol.* S4,B,4,5; S5, A,1,2; NKF. *Am J Kidney Dis*. 2006;47(suppl 3): S59,A,2; EPOGEN® PI, 4/09 v21:15,A,7; 27,A,6.]**Absolute iron deficiency can occur with increased blood loss common to dialysis, laboratory testing, and surgeries. **[Fishbane S, et al. *Handbook of Dialysis.* 3rd ed. 2000:488,A,4; NKF. *Am J Kidney Dis.* 2001;37(suppl 1):S59,A,2; Kwack C, et al. *Semin Dial*. 2006;19: 147,B,1]** Functional iron deficiency can occur during infection, when iron is not released from its stores in the RES and the liver. [**Wish JB. *Clin J Am Soc Nephrol.* 2006;1: S5,A,2; NKF. *Am J Kidney Dis*. 2006;47(suppl 3): S59, B1; Kwack C, et al. *Semin Dial.* 2006;19: 147,A,3]]** Patients taking EPOGEN® (Epoetin alfa) therapy may also experience functional iron deficiency, presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. **[EPOGEN® PI, 4/09 v21:15,A,7; Stivelman JC. *Dialysis Therapy*. 3rd ed. 2002:326,A,3-326,B,1; Fishbane S, et al. Handbook of Dialysis. 3rd ed. 2000:482,A,4;]**

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4. INFECTION AND INFLAMMATION

Patients with chronic renal failure, or CRF, who are on dialysis, have an increased risk of infection. **[Vanholder R. *Clinical Dialysis*, 4th ed. 2005:Ch18: 515, A,1 B,1 and 516-520 section headings; Breiterman-White R. *Nephrol Nurs J.* 2006;33: 320, table 2]** The immune system responds to infection by releasing cytokines such as tumor necrosis factor and interleukins. **[Weiss G. *N Engl J Med.* 2005;352:1011, A,2; 1015, table 2; Kwack C, et al. *Semin Dial*. 2006;19: 148,B,1]** It has been shown that when these cytokines are released, they inhibit erythropoietin production and inhibit the proliferation and maturation of red blood cell precursors, leading to a lower production of red blood cells and reduction in hemoglobin levels. **[Weiss G. *N Engl J Med.* 2005;352:1014, B,1,3; Kwack C, et al. *Semin Dial*. 2006;19: 148,B,1; Gunnell J, et al. *Am J Kidney Dis*. 1999;33:69,B,1; Fishbane S. Semin Dial. 1999;12: 6,A,4.]**

Additionally, infection and inflammation has an impact on two key proteins, called transferrin and hepicidin. Transferrin, which carries iron to the red blood cell precursors, is suppressed. **[Weiss G. *N Engl J Med.* 2005;352:1016, Table 3; Gunnell J, et al. *Am J Kidney Dis*. 1999;33:68, A,1]** Hepcidin levels, which regulate iron absorption and tissue storage, are elevated. Elevated hepcidin levels during infection cause a decrease in iron release from its stores. **[McGrath H Jr, Rheumatology. 2004;43:1323,A, 1,2 and Table 1; Pertosa G, et al. *J Am Soc Nephrol.***

2005;16:476A,B,1,2. Vyoral D, et al. Int *J Biochem Cell Biol.* 2005;37:1770,B,3;1771,A,1; Weiss G. *N Engl J Med.* 2005;352:1014, A,1]

This results in a temporary sequestration of iron in the macrophages of the RES and in the liver cells, where iron is stored as ferritin. This sequestration is known as a "blockade" and leads to a decreased blood iron concentration and diminished availability of iron. **[Andrews NC*. J Clin Invest.* 2004;113: 1252,A,fig 1;1251,C,2; Gunnell J, et al. *Am J Kidney Dis*. 1999;33: 69,B,1; Wish JB. *Clin J Am Soc Nephrol*. 2006;1 S5,A,2; Fishbane *S. Semin Dial.* 1999;12: 6,A,4.]**

Consequently, there may be an increase in ferritin levels—reflecting the iron stored in the liver. Simultaneously, a decrease in transferrin-bound iron in the bloodstream is reflected by the low to normal TSAT—or transferrin saturation—levels. [**NKF. *Am J Kidney Dis.* 2006;47(suppl 3): S58,A,2; B,1; Barth RH. *Semin Dial*. 1999;12:227,B, 1-3;**
Hutson PR. In: Lee M, ed. *Basic Skills in Interpreting Laboratory Data*. 2004:chap 15. 454, A,3-5]Therefore, despite the fact that there may be adequate iron stores in these patients, their anemia may be more difficult to manage. **[Gunnell J, et al. Am J Kidney Dis. 1999;33: 69,B,1; NKF. *Am J Kidney Dis*. 2006;47(suppl 3): S59, A4,B1 ;Hutson PR. In: Lee M, ed. *Basic Skills in Interpreting Laboratory Data*. 2004:chap 15. 454, A,3-5]**

225Words

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