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2022 CONTINUING MEDICAL EDUCATION GRANTS

Name of Recipient	Program Name	Program Description	Amount
Creative Education Concepts	Breaking the Cycle in Cardiorenal Anemia Syndrome The Practice-Changing Role of IV Iron at the CKD – Heart Failure Interface	**Activity Overview** This educational grant request for our company to develop and deliver an ACCME-accredited enduring activity to be hosted on Medscape, tentatively titled, "***Breaking the Cycle in Cardiorenal Anemia Syndrome: The Practice-changing Role of IV Iron at the CKD–Heart Failure Interface***." Also included in the proposal is our CEC Clinical TouchPoints that will extend the reach of the Medscape activity through a 12-month CEConversations podcast with a total reach of 1,000 learners for this initiative. This educational initiative is targeted to nephrologists, cardiologists, and primary care physicians who help manage patients with cardiorenal anemia syndrome, including non–dialysis-dependent chronic kidney disease (NDD-CKD), heart failure (HF), or both. To be delivered as an enduring modality on Medscape.org and as a CEConversations podcast, this session will offer attendees pathophysiologic context for cardiorenal anemia syndrome (CRAS), including a concerted focus on NDD-CKD and HF, and take a deep dive into the established, emerging, and practice-changing role of IV iron in the CRAS management paradigm. Practical, case-based elements will be offered that provide attendees with real-world examples of IV iron safety, efficacy, and the need for multidisciplinary (nephrologist-cardiologist-PCP) care. **Pathophysiologic Foundations of ID/IDA in CRAS: The Pivotal Roles of Inflammation and Hepcidin** Iron, an essential trace element, is integrally involved in numerous human biological processes. Dietary iron is absorbed and distributed via plasma transferrin for utilization by the muscle, liver, bone, and blood stores.47 Iron is centrally involved in erythropoiesis and oxygen transport, delivery, and utilization. Iron homeostasis represents a careful balance of dietary intake and losses, and as we obtain a more accurate and intricate picture of the biochemical and microbiological mechanisms governing iron metabolism, we see that a 25-peptide molecule known as hepcidin represents the central fulcrum.48 In practical terms, hepcidin is a polypeptide produced by liver hepatocytes that serves as the master regulator of systemic iron metabolism and is centric to nearly all physiologic iron homeostatic mechanisms. As such, it is inherently a critical and influential component of IDA pathophysiology, especially in the setting of hyperinflammatory conditions such as CKD and HF.49 Hepcidin is upregulated by circulating and tissue iron, cytokine-based crosstalk between liver sinusoidal cells, and perhaps most notably, by proinflammatory cytokines such as IL-6.49 Conversely, hepcidin levels are inhibited by iron deficient states, expansion of erythropoiesis, and anemia/hypoxia, among other factors.50,51 The following figure provides graphical insights into how hepcidin regulation, and subsequently iron homeostasis and metabolism, are characterized in the setting of inflammation (i.e., in the presence of increased IL-6 levels); the central dogma is that inflammation promotes production of IL-6, which then leads to increased hepcidin levels, which then blocks macrophage iron release and decreases intestinal absorption of iron, thereby leading to functional iron deficiency (FID) and subsequent IDA.52	$ 142,150 Paid 8/4/22 ACH

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2022 CONTINUING MEDICAL EDUCATION GRANTS

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Pharmacy Times Continuing Education	*An ASHP Midyear Satellite Symposium* Exploring the Efficacy and Safety of Iron Replacement Therapies for the Treatment of Iron Deficiency Anemia in Chronic Kidney Disease: A Review for Health Systems Pharmacists	Due to the combination of reduced iron absorption and increased iron losses, iron deficiency is common among patients with chronic kidney disease (CKD) who are both non-dialysis (ND) and dialysis dependent. (Gafter-Gvili 2019) Patients with CKD have an elevated risk of cardiovascular disease (CVD), with rates of mortality due to CVD representing the leading cause of death in this patient population. Often multifactorial in their etiologies, iron deficiency (ID) and iron deficiency anemia (IDA) are significant complications of CKD and end stage renal disease (ESRD) that may develop early in the course of the disease and progress with loss of renal function. (NKF 2006, SABM 2022) The prevalence of anemia increases across the advancing stages of CKD, with estimates anywhere from 7% to >50% in the more advanced stages of the disease. (Batchelor 2020) Around 70% of the iron in adults is found within hemoglobin in red blood cells so anemia is the most readily established result of iron deficiency; however, it is now apparent that iron deficiency in the absence of anemia also has adverse consequences. (Balendran 2021) Since anemia is associated with augmented risk of morbidity and mortality, early identification and initiation of treatment of iron deficiency is critical to the efficacious management of anemia in individuals with CKD, particularly those with kidney failure needing replacement therapy such as dialysis or transplantation. (Gutierrez 2021) The treatment of anemia due to CKD includes transfusion support, erythropoietin stimulating agents (ESA) and iron therapy. Evidence suggests that aggressive treatment of iron deficiency anemia earlier in the progression of CKD can improve quality of life (QOL) as well as disease outcome and may possibly slow the progression to complete renal failure. (SABM 2022) The incidence of anemia increases in more advanced stages of CKD. Left untreated, anemia is correlated with some adverse effects on cardiac function, quality of life, progression of CKD and overall survival. Patients with CKD are also at greater risk for cardiovascular issues such as coronary artery disease, heart failure, arrhythmias and sudden cardiac death. (Jankowski 2021) The development and approval of novel iron replacement products particularly intravenous iron replacement products have provided numerous new tools to effectively address iron deficiency and iron deficiency anemia in patients with CKD. Oral and intravenous iron agents are both available to replenish iron in patients with CKD diagnosed with ID and IDA. Chronically elevated circulating concentrations of hepcidin limit gastrointestinal absorption of iron, impeding the efficacy of oral iron supplements in patients with CKD and because of this intravenous (I.V.) iron infusion is a pillar in the treatment of iron deficiency in CKD, particularly in individuals with kidney failure needing replacement therapy, who almost exclusively receive I.V. iron. (Gutierrez 2021) The selection of which agent to use is most often influenced by goals of therapy, tolerability, convenience, and response to prior therapy. While there are therapies for anemia in CKD, the current clinical evidence suggests that this condition is both underdiagnosed and undertreated in clinical practice. The reasons for these gaps may be because patients with early stage CKD often exhibit only mild or no visible symptoms and as a result the disease commonly remains undiagnosed and untreated until it has reached an advanced stage which is linked with significantly elevated rates of morbidity and mortality when compared to the earlier stages of the disease. (Hao 2020) To effectively manage IDA in patients with CKD, having a thorough understanding of its pathophysiology and the treatment options is essential. As integral members of the healthcare team, it is imperative for pharmacists to be knowledgeable about the etiology, risk factors and clinical presentation associated with CKD, the various stages of CKD and the related complications including a host of cardiovascular disease related complications and the augmented risk of ID and IDA. Ongoing continuing education will enable health systems pharmacists to gain a greater understanding about CKD, related complications and the efficacy and safety of IV iron replacement products, the advantages of IV formulations over oral iron products as well as expand knowledge about their use in the treatment of CKD patients with iron deficiency anemia. Equipped with expanded knowledge, health systems pharmacists can aid in identifying patients who may be ideal candidates for IV iron therapy, evaluate IV iron replacement treatments in different patients who may be at higher risk for the development of anemia in CKD and can develop strategies to help mitigate those risks, thus lowering burdens associated with both CKD and IDA on individual patients and on healthcare resource utilization.	$ 142,850 Paid ACH 8/5/2022

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2022 CONTINUING MEDICAL EDUCATION GRANTS

Name of Recipient	Program Name	Program Description	Amount
Pri-Med Institute	**Lifting the Veil: Recognizing and Managing Iron Deficiency and Iron Deficiency Anemia in Inflammatory Bowel Disease**	Iron deficiency (ID) and iron deficiency anemia (IDA) are well-documented complications in IBD, estimated to occur in up to 90% and 76% of patients, respectively.6–9 Iron deficiency is the most commonly occurring nutritional deficiency worldwide,9 while, IDA is believed to be the most prevalent extraintestinal manifestation of IBD.10,11 The consequences of ID and IDA—primarily fatigue, lethargy, reduced concentration, dizziness, tinnitus, pallor, and headache—can be significant and add to the already considerable quality of life burden associated with IBD.10,12–14 Importantly, ID can cause symptoms with the presence or absence of anemia.14 There is also a strong relationship between these conditions and depression in patients with IBD.9,12 Further, the presence of anemia has been shown to be an independent predictor of poor outcomes (hospitalization and surgeries) and healthcare resource utilization (visits to gastroenterology clinics, telephone calls) in patients with IBD.10 Given the enormous impact of anemia on patient quality of life and clinical outcomes, treatment of anemia has become an independent treatment target and quality metric in IBD.15 Multiple factors contribute to the development of anemia in patients with IBD, but IDA is the most frequent cause, reported in up to 90% of all anemic patients with IBD.11,13,15,16 Iron deficiency in IBD occurs due to blood loss through ulcerations of the intestinal mucosa, reduced iron intake, and reduced iron absorption due to increased hepcidin production.11, 15, 17 Hepcidin is an acute-phase protein that plays a crucial role in controlling iron availability to tissues by binding to ferroportin and preventing iron entry into plasma.4,18 Hepcidin expression is upregulated during infection and inflammation, such as occurs in active IBD, leading to reduced iron absorption in the duodenum and reduced iron availability for heme formation in the bone marrow.19 Accordingly, hepcidin expression has an inverse relationship with plasma iron concentrations.4 Given this relationship, it is not surprising that serum hepcidin correlates positively with disease activity and negatively with ferroportin in patients with IBD.20 ***Defining ID and IDA.*** Although ID may exist with or without anemia, ID is not consistently recognized as a distinct disorder from IDA.8, 9 Moreover, there is considerable variability in the definitions of ID proposed in the literature. Numerous guidelines for the diagnosis and management of ID have proposed thresholds of serum ferritin for defining ID across various populations, ranging from 12-15 µg/L in the generation population to 200 µg/L in patients with CKD who are receiving hemodialysis.9 Guidelines specific to patients with IBD have defined 30 µg/L as the ferritin threshold for defining ID in those without inflammation and 100 µg/L for those with active disease.21, 22 In contrast, anemia is defined by the World Health Organization (WHO) is a decline in blood hemoglobin to a concentration of <12 g/dL in women and <13 g/dL in men, with varying thresholds based on age, sex, pregnancy, altitude, and smoking.23 ***Screening for ID and IDA.*** Despite variation in definitions for ID and IDA, screening for both conditions in IBD patients is recommended.15, 24 The Anemia Care Pathway developed by the Crohn's and Colitis Foundation (CCF) recommends screening for anemia using the WHO definitions based on gender as well as patient-reported symptoms, such as fatigue and clinical gastrointestinal (GI) bleeding.15 Recognizing the association between ID and fatigue in IBD, the committee also recommended universal ferritin screening to identify ID in this population.15 Other experts recommend that ferritin and transferrin saturation be used concomitantly to improve early detection of ID and prevent anemia.24 To that end, regular measurement of iron status biomarkers (hemoglobin, ferritin, transferrin saturation) to allow early diagnosis and prompt treatment of ID and IDA has been proposed as part of treat-to-target strategy for IBD management.24	$ 228,353 Paid ACH 9/1/2022

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Name of Recipient	Program Name	Program Description	Amount
PRO CE, LLC	AMCP Nexus 2022: Iron Deficiency: Managed Care Considerations for Optimizing Evidence-Based and Cost-Effective Use of IV Iron Replacement Therapies	Iron deficiency anemia is the most common cause of anemia worldwide, which results in microcytic and hypochromic red cells on the peripheral smear.[Warner 2021] The cause of iron deficiency anemia varies based on age, gender, and socioeconomic status. Iron deficiency may result from insufficient iron intake, decreased absorption, or blood loss. Iron deficiency anemia most often occurs due to blood loss, especially in older patients. It also may be observed with low dietary intake, increased systemic requirements for iron such as pregnancy, and decreased iron absorption such as in celiac disease.[Warner 2021] Typical symptoms of iron deficiency anemia include fatigue, pica (ie, pagophagia, ice craving), restless leg syndrome, headache, exercise intolerance, exertional dyspnea, and weakness.[Lopez 2016] Iron deficiency also often is associated with chronic diseases. It is estimated to affect 37% to 61% of patients with HF, 24% to 85% of patients with CKD, and 13% to 90% of patients with IBD.[Peyrin-Biroulet 2015; Jankowska 2010; Klip 2013; Okonko 2011; McClellan 2004; Yeo 2014] To complicate matters, symptoms such as fatigue are commonly seen in these conditions, which can mimic and be confused with symptoms of iron deficiency anemia. Consequently, the management of iron deficiency anemia often can be overlooked. Untreated iron deficiency anemia can have greater consequences in these diseases, causing an exacerbation of the underlying disorder.[Cappellini 2017] Treatment of iron deficiency anemia in chronic conditions such as HF, CKD, and IBD consists of iron replacement therapy, and IV iron formulations have profoundly impacted the management of individuals with iron deficiency anemia and concomitant chronic disorders. Several IV iron formulations are available, including ferric carboxymaltose, ferric gluconate, ferumoxytol, iron sucrose, ferric derisomaltose, and low molecular weight iron dextran. Managed care pharmacists must understand the role of IV iron in treating patients with chronic diseases and iron deficiency anemia, with a strong consideration for effective healthcare resource utilization. The literature has identified notable educational gaps among HCPs providing care for these patient populations. As such, this educational activity will review the role of IV iron replacement in iron deficiency anemia and accompanying chronic conditions and focus on the economic burden of these diseases and the impact of IV iron on healthcare resource use.	$ 155,000 PAID ACH 09/14/2022