A.13	Deferiprone – transfusional iron overload – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended **Justification**: Patients with different types of anemia, such as aplastic anemia, thalassemia, sickle cell disease (SCD) and myelodysplastic anemia, who become dependent on transfusions will undoubtedly develop long-term iron overload. Indeed, as humans are not physiologically capable of excreting additional iron, blood transfusion therapy leads to the accumulation of iron in the body. This iron overload is a major concern for patients who receive approximately 10 to 20 or more units of blood. It is associated with multi-organ damage particularly to the liver and heart, and ultimately premature death in the absence of specific treatment. Iron chelators have become increasingly important in medicine in recent years, due to promising results in their individual and/or combined use for the treatment of iron overload. Several trials have shown the safety and efficacy of chelation therapy in transfusional iron overload in adult and pediatric patients with major thalassemic syndromes, SCD, or other chronic anemias. Iron chelation therapy appears to restore iron balance and reduce the risk of mortality. Specific iron chelators include deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX). Currently, there are two iron chelators on the WHO model lists: DFO in EML and EMLc and DFX as an alternative therapy to DFO. DFP was the first orally available iron chelator. It is currently used in over 50 countries. DFP is generally well tolerated, with an acceptable safety profile. DFP is effective in cardiac iron clearance and has also been shown to reduce serum ferritin and liver iron. In addition, it can be used in combination with other chelating agent. DFP is also a cost-effective option and reduces the economic burden on the health care system.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable **Comments**: The most common hematologic causes of iron overload are myelodysplastic syndromes, SCD, and thalassemia. The latter are potentially fatal inherited hemoglobinopathies that cause severe anemia. The WHO recognizes SCD as a global public health problem. In 2019, it was estimated that approximately 6 million people have SCD. With regard to thalassemic syndromes, approximately 60.000 children are born with symptomatic forms of the disease each year. The prevalence is highest in the Mediterranean region, the Middle East, Central Asia, India, South China, East and Southeast Asia, and for thalassemic syndromes, more than half of the cases live in sub-Saharan Africa or India, low-income countries. A major cause of morbidity in these patients is iron overload due to repeated red blood cell transfusions, which is a cornerstone of therapeutic management. Untreated or inadequately treated iron overload leads to complications such as liver cirrhosis, hepatocellular carcinoma, cardiomyopathy, and endocrine disorders such as hypothyroidism, diabetes, gonadal insufficiency, and growth retardation.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable **Comments:** Despite the fact that total iron excretion using DFP is a bit less, compared to that of DFO, DFP cardioprotective effect is better than DFO. DFP is very efficient in eliminating extra iron from the organs, especially the heart since DFP is able to penetrate the cell membrane. A retrospective survey demonstrated that the administration of DFP over time improves the cardiac ejection fraction. Additionally, in studies based on epidemiological data, mortality and morbidity in cardiac events were lower in individuals taking DFP. Also, oral DFP was observed with superior effects on SCD morbidity. A study aimed to evaluate the reduction of hepatic and cardiac iron assessed through T2 magnetic resonance imaging. The results for the most efficient iron chelator in reducing myocardial iron and hepatic iron were DFP and DFO, respectively. The introduction of effective iron chelation therapy has been shown to correlate with improved survival, quality of life, and reversal of hepatic and cardiac functional complications in patients with thalassemia. But long-term clinical trials, even not designed to assess endocrine disease, has not been shown to reverse diabetes or hypothyroidism, secondary to iron overload. There is a paucity of data published on the efficacy and benefit of DFO in the specific setting of MDS patients, and data from the thalassemic population cannot be translated.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable **Comments**: DFP is generally well tolerated, with an overall safety profile. The most significant side effects is agranulocytosis typically occurring in the first year of treatment, reported in 1% to 2% of patients treated with DFP. Less severe episodes of neutropenia occurs in 5% of treated cases. The mechanism through which DFP causes agranulocytosis has been unknown to date. Most neutropenia and agranulocytosis cases resolved within 4 to 12 days of treatment discontinuation. Other less frequent/severe adverse events include gastrointestinal symptoms (nausea, abdominal pain, vomiting), arthralgia, musculoskeletal pains, transient changes in liver enzymes and zinc deficiency. Approximately 10% of patients stop using the drug permanently due to its side effects
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☐ No ☐ Not applicable **Comments:** Cases receiving DFP treatment should be strictly followed up by taking a complete blood count weekly. Notably, 3 of 4 neutropenia cases reported occurred in the first 6 months of therapy. The necessity to monitor blood count weekly therefore appears to decrease after the first 6 months of therapy. Given that weekly monitoring can be burdensome, it is proposed that monitoring fortnightly might be recommended without compromising safety.

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☐ No ☐ Not applicable **Comments**: Iron chelation should start when patients have received 10 transfusions, have serum ferritin >1000 lg/L, at least 2 years of age. Once treatment is started, iron overload status should be monitored after 6 months and then every 6 to 12 months. Serum ferritin levels should be monitored every 3 months. Dose escalation should be considered in patients with serum ferritin level 1500–2000 ng/mL (if LIC measurement is unavailable) after 6 months treatment. The usage of combination and consecutive chelating agents can enhance efficiency and decrease the incidence of adverse events.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable **Comments:** DFP was found to be the most cost-effective of the chelation regimens in beta-thalassaemia. DFP was demonstrated to have the potential to result in cost-savings and QALY gains for the Chinese healthcare system. There are substantial differences in costs between countries (regions).
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☐ No ☐ Not applicable **Comments:** The is a large availability on the originator of DFP. Generic DFP is also available in the majority of the countries.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable **Comments:** There are no published WHO-specific guidelines regarding the treatment of iron overload due to blood transfusions