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Class Update: Iron Chelators

Month/Year of Review: June 2015 **Date of Last Review:** June 2012

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Since the last update in 2012, a new formulation of deferasirox (Jadenu™) was approved by the FDA. This drug class has not been reviewed since June 2012.

Research Questions:
1. Is there any new comparative evidence regarding the efficacy of iron chelators for iron overload in patient with thalassemia syndromes?
2. Is there any new comparative evidence of harms associated with iron chelators used to treat iron overload?
3. Are there subgroups of patients based on demographics (ie, age, race, gender), comorbidities (ie, drug-disease interactions), or other medications (ie, drug-drug interactions) for which one iron chelator may be shown to be more efficacious or more harmful than another?

Conclusions:
- There is low quality evidence of no differences in mortality or hepatic fibrosis scores between iron chelators.
  Liver and Myocardial Iron Concentration
- There is low quality evidence that use of 30 mg/kg of deferasirox may result in a larger mean reduction in liver iron concentration (LIC) than deferoxamine (MD 2.50; 95% CI 0.54 to 4.62, p=0.01).
- There is also low quality evidence that LIC is reduced more in patients who take deferiprone versus deferoxamine after 12 months (ratio of geometric means 1.49; 95% CI, 1.06 to 2.09), after 24 months (1.45; 95% CI, 0.90 to 1.80), and after 30 and 34 months (0.51; 95% CI, 0.36 to 0.71).
- There is low quality evidence that combination of deferiprone and deferoxamine compared to deferoxamine monotherapy is more effective in reducing myocardial iron concentration (SMD 2.68, 95% CI 1.96 to 3.40, p<0.00001).
  Left Ventricular Ejection Fraction (LVEF)
- There is low quality evidence that combination therapy of deferiprone with deferoxamine improves LVEF to a greater extent than either agent alone (MD 5.67; 95% CI, 1.21 to 10.02, p=0.008).
- There is low quality evidence that deferiprone results in a greater percent change in LVEF from baseline compared to deferoxamine (MD 2.88; 95% CI, 1.12 to 4.64, p=0.001). Mean LVEF was higher with deferiprone and deferoxamine used in combination compared to either agent alone (78.04±8.6% vs. 67.4±9.8%; and 68.4±4.7% vs. 65.3±6%; WMD 3.37; 95% CI, 0.79 to 5.95, p=0.01).

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- There is low quality evidence that patients who receive deferoxamine may have a lower risk of experiencing an adverse event compared to patients who deferiprone (RR 0.45; 95% CI, 0.24 to 0.84).

Recommendations:
- Designate deferasirox (Jadenu™) as a non-preferred agent. No changes to the preferred drug list (PDL) needed.

Previous Conclusions and Recommendations:
- There is insufficient evidence to compare the efficacy of deferiprone with the other oral agent, deferasirox.
- Deferiprone represents the only option for patients for whom deferoxamine and deferasirox are contraindicated or prove to be inadequate in reducing iron burden.
- Recommend adding deferoxamine as a preferred agent on the PDL.
- Recommend making the oral agents deferasirox and deferiprone non-preferred and using the default non-preferred PA criteria to utilize them as second line agents.

Background:
Iron chelators are agents that bind to and reduce plasma levels of iron. In patients with iron overload, such as those with thalassemia or other conditions which require regular blood transfusions, excess iron in the blood can occur which results in damage and disruption of organ function due to iron's free-radical generating properties. Excess iron is mainly stored in the liver but can redistribute to the heart and endocrine tissues leading to sudden cardiac death, arrhythmia, heart failure, liver cirrhosis, or endocrine dysfunction. Iron chelation is used to prevent iron overload and iron's detrimental oxidizing activities on organs. Significant outcomes of interest for iron chelators are mortality, cardiac function (i.e. ejection fraction), and histological evidence of hepatic fibrosis. Unfortunately the majority of the available studies limited to less clinically relevant outcomes of measures of iron overload such as liver iron concentration, myocardial iron concentration, serum ferritin, and urinary iron excretion.[1]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A systematic review of RCTs which compared deferiprone to deferoxamine, or a combination of both compared to each drug as monotherapy for reduction of iron overload in chronically transfused patients with β-thalassemia, was assessed.[1] The outcomes of mortality, reduction of end-organ damage, and measures of organ-specific iron overload in chronically transfused patients were assessed. A priori criteria were established before the conduct of review. Inclusion and

exclusion criteria were explicitly stated and agreement between two independent assessors was calculated. Disagreements were resolved by consensus. A list of included studies was provided, although a list of excluded studies could not be found. Forty-three full-text articles were assessed for eligibility after screening; 8 studies were excluded as they did not measure outcomes of interest, and 7 studies were not RCTs. Thirteen citations were merged with their primary article resulting in 13 included RCTs. Characteristics of the included studies were adequately described and quality of each study was assessed utilizing the GRADE tool. The quality of evidence for all included studies was rated as low. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. Reporting bias was reported to be examined by visual inspection of funnel plots, but was not made available. Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. Deferiprone was found to be more efficacious than deferoxamine in improving cardiac ejection fraction, defined as change from baseline LVEF% (MD 2.88; 95% CI, 1.12 to 4.64, p=0.001) based on the results of one study. Another study of patients on deferiprone 75 mg/kg/day by mouth three times weekly or deferoxamine 30-40 mg/kg/day subcutaneously seven days a week found endocrine dysfunction, defined as bone mineral density (BMD) and pubertal status according to Tanner's stages, had progression from Tanner's stage 1 to 2 or 3 in all patients and an improvement in BMD (MD 0.09, 95% CI 0.08 to 0.10, p<0.00001). The combination therapy was found to be more efficacious than either monotherapy in improving cardiac ejection fraction (MD 5.67, 95% CI 1.21 to 10.02, p=0.008). No significant difference was found in other outcomes including mortality, hepatic fibrosis score at the end of treatment, LIC, and change from baseline serum ferritin. Myocardial iron content by cardiac MRI was reported in two studies but pooling of data was not possible. The results of the review indicate that available evidence is of low quality and that more high-quality, large RCTs measuring clinically relevant outcomes are needed before it can be shown that deferoxamine is superior to deferiprone or vise-versa.[1]

A systematic review of RCTs in which the clinical effectiveness profile of iron chelators for patients with transfusion-dependent thalassemia major was assessed.[2] Outcomes assessed included ejection fraction, change in LIC, change in myocardial iron concentration, change in serum ferritin, and change in urinary iron excretion. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated and phase 2 cross-over trials and studies that presented poor data or case reports were excluded. There had to be agreement between two independent assessors. A list of included studies was provided, although a list of excluded studies could not be found. Thirty-seven full-text articles were assessed for eligibility after screening. Sixteen articles were used for meta-analysis. It was not explicitly stated why 21 studies were excluded. Deferiprone, deferoxamine, and deferasirox were compared with each other as monotherapy, combinations, or when sequentially administered. Of the included studies, 1520 patients aged 5-50 years with transfusion-dependent thalassemia major in any setting worldwide made up the patient population in the review. The GRADE tool was used to rate the quality of included studies and their process was outlined. The quality of evidence for all studies included was rated as low. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. It was stated that due to a low power to detect true heterogeneity in a low number of studies, a cut-off p-value of 0.10 was used. It was stated that a bias defined as "free of selective reporting" was examined but was found to be "unclear in 70.4% of the trials with no graphical aids being offered". Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. Combination therapy of deferiprone and deferoxamine versus monotherapy of either drug resulted in lower final LIC, defined as change in LIC (mcg/g dry weight) from baseline to end of treatment (p<0.0001), and increased serum ferritin levels, defined as change in ferritin levels from baseline to end of treatment. Serum ferritin as the difference between final and basal values was significantly increased in patients receiving deferasirox 5, 10, and 20 mg/kg versus deferoxamine 30, 35, and 30 mg/kg respectively (95% CI 544.71 to 1411.29, p<0.00001; 95% CI 565.98 to 1036.02, p<0.00001; and 95% CI 121.65 to 534.35, p=0.002). Ejection fraction was significantly higher in sequential deferiprone and deferoxamine groups compared to deferoxamine monotherapy in one study (78.04±4.12% vs. 69.02±6.05%; weighted mean difference (WMD) 9.02, 95% CI 6.4 to 11.64, p<0.00001). Ejection fraction was significantly higher in deferiprone and deferoxamine combination therapy groups compared to monotherapy of either agent in two trials (78.04±8.6% vs. 67.4±9.8%; and 68.4±4.7% vs. 65.3±6%; WMD 3.37, 95% CI 0.79 to 5.95, p=0.01). Urinary iron excretion (mg/kg/day) was measured in two trials and was significantly higher in patients receiving deferiprone plus deferoxamine versus patients receiving monotherapy of either agent trials (0.88±0.32 vs. 0.38±0.22; and 7.37±1.89 vs. 5.83±1.65; WMD 1.28, 95% CI 0.53 to 2.02, p=0.0008) and in patients receiving sequential deferiprone and deferoxamine compared with deferiprone alone (0.76±0.49 vs. 0.53±0.21; WMD 0.23, 95% CI 0.04 to 0.42, p=0.02).

No significant difference was found in the outcome of myocardial iron concentration at the end of intervention. In many of the other outcomes heterogeneity was not proven to be statistically significant. In all outcomes, GRADE quality of evidence was low. The authors stated that their findings did not support any specific chelation treatment. The results of the review indicate that the available evidence is limited and of low quality and that more high-quality, large RCTs measuring clinically relevant outcomes are needed before it can be shown that associated and sequential deferiprone plus deferoxamine treatment can be deemed effective in clinically significant outcomes.[2]

A systematic review with meta-analysis of 16 RCTs was also conducted that compared deferiprone, deferoxamine, and deferasirox in patients with severe thalassemia.[3] The outcomes of difference in serum ferritin from baseline to intervention, difference in LIC from baseline to intervention, myocardial iron concentration, and LVEF, were assessed. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated and agreement between two independent assessors was reached with differences resolved by a third reviewer. A list of included studies was provided, although a list of excluded studies could not be found. Forty-six articles were assessed for eligibility after screening; 30 studies were excluded as they did not have relevant results or were deemed to have used inappropriate comparisons between groups. Characteristics of the included studies were not adequately described although the quality of each study was assessed utilizing the Risk of Bias Tool evaluation following the recommendations from the Cochrane collaboration. Only three of the studies used double blinding and only four used concealed allocation. Only one of the studies presented the completed outcome data. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. Reporting bias was graded as low, unclear, or high and was reported in a table but a funnel plot was not used since the study samples of each comparison were not sufficient making publication bias unclear. Trial sponsorship and conflicts of interest were not explicitly stated for either the review itself or the included studies. Eleven studies presented serum ferritin changes as an outcome. Although types of interventions, treatment duration, and number of participants of included studies were outlined, the doses used in the treatments were not explicitly stated except when indicated in the results of the outcomes. One study reported that combination therapy of deferoxamine and deferiprone reduced serum ferritin significantly compared to deferoxamine alone (standardized mean difference (SMD) 0.45, 95% CI 0.01 to 1.48, p=0.05). Another study found deferasirox decreased serum ferritin more than deferoxamine (MD 538.03, 95% CI 177.39 to 900.68, p=0.003). A subgroup analysis of the same study was performed on different doses of deferasirox and changes in serum ferritin were not observed in the 5 mg/kg or 10 mg/kg doses but were observed in the 20 mg/kg and 30 mg/kg doses. No other statistically significant differences were observed. Eights studies reported the outcome of LIC. In one study, reduction in patients taking 30 mg/kg of deferasirox had a larger mean difference in LIC at end of intervention compared to deferoxamine (MD 2.50, 95% CI 0.54 to 4.62, p=0.01). No other statistically significant differences were observed. Five studies reported myocardial iron concentration and found there to be a statistically significant difference in at the end of treatment between deferiprone and deferoxamine (SMD -0.35, 95% CI -0.63 to -0.08; p=0.01). One of the studies showed combination of deferiprone and deferoxamine compared to deferoxamine monotherapy to be more effective in changing myocardial iron concentration (SMD 2.68, 95% CI 1.96 to 3.40, p<0.00001). Five trials reported outcomes of LVEF. A significant reduction of LVEF was seen in deferiprone groups when compared to deferoxamine groups (SMD -0.35, 95% CI -0.60 to -0.10, p=0.007) and combination of deferoxamine and deferiprone compared to deferiprone monotherapy (SMD -0.70, 95% CI -1.16 to -0.23, p=0.003). The results of the review indicate that available evidence is of low quality and that more high-quality, large RCTs measuring clinically relevant outcomes are needed before it can be shown that any one iron chelator is more safe of effective than another.[3]

A systematic review of RCTs which evaluated the effectiveness and safety of oral deferasirox in people with sickle cell disease (SCD) and secondary iron overload was assessed.[4] The primary outcome assessed was mortality. Secondary outcomes included reduced end-organ damage due to iron deposition, measures of iron overload, measures of iron excretion over 24 hours, adverse events, participant satisfaction, and cost of intervention per year. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated and cross-over studies and non-inferiority studies were excluded. One author screened all titles and abstracts of identified papers for relevance and a second author independently screened full papers and identified relevant studies for

inclusion. Disagreement was resolved via consensus or through a third party. A list of included studies was provided, although a list of excluded studies could not be found. Twenty-five full-text articles were assessed for eligibility after screening. One study included in a previous review in addition to one new study were used for the analysis. Seven articles were excluded because they were a review or editorial or other form of published article. One was excluded because it included deferasirox. Fourteen were excluded due to observational data being assessed. One article was a cost-effectiveness analysis and another was excluded because it compared hydroxyurea/phlebotomy to transfusions/chelation. In both studies patients either received deferasirox or deferoxamine. The quality of each study was assessed utilizing the Risk of Bias Tool evaluation following the recommendations from the Cochrane collaboration and the evidence was evaluated using the GRADE assessment tool. The characteristics of the patients in the original studies were fully outlined. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. Risk of bias was stated to be high for both studies since they were classified as open-label trials. Since only two studies were used in the review, funnel plots were not used to assess publication bias. Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. There were only limited data presented on the primary outcome as only one study reported death with one occurrence in the deferasirox group (RR 1.26, 95% CI 0.05 to 30.41). No significant differences were seen in the outcomes of reduced end-organ damage due to iron absorption. Ferritin reduction was reported to be significantly greater in patients treated with deferoxamine at the end of both studies (MD of change 440.69 mcg/L, 95% CI 11.73 to 869.64). No data were available on iron excretion in urine or feces. Adverse events of any kind were stated as being reported significantly more often in the deferoxamine group although the reported statistics does not agree with this statement (RR 0.88, 95% CI 1.03 to 5.55). Serious adverse events occurred with similar frequency in both groups. Participant satisfaction with treatment, convenience, and likelihood to continue therapy were significantly higher in deferasirox patients compared to deferoxamine patients (RR 3.13, 95% CI 1.99 to 4.93; RR 3.85, 95% CI 2.28 to 6.47; and RR 6.86, 95% CI 3.38 to 13.00; respectively). Overall rate of discontinuations were lower in patients taking deferasirox (RR 0.53, 95% CI 0.31 to 0.92). No data were available on the cost of either intervention. The authors concluded that there are little data on relevant outcomes such as mortality and end-organ damage. More long-term studies on the effects of deferasirox in patients with SCD are needed in order to establish optional treatment.[4]

A systematic review of RCTs evaluated the effectiveness and safety of oral deferasirox in people with thalassemia and secondary iron overload.[5] The primary outcome assessed was mortality. Secondary outcomes included reduced end-organ damage due to iron deposition, measures of iron overload, measures of iron excretion over 24 hours, adverse events, participant satisfaction, and cost of intervention per year. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated and cross-over studies and non-inferiority studies were excluded. One author screened all titles and abstracts of identified papers for relevance and two authors then independently screened full papers and identified relevant studies for inclusion. Disagreement was resolved via consensus or through a third party. A list of included studies was provided, although a list of excluded studies could not be found. Two-hundred eighty-nine full-text articles were assessed for eligibility after screening. Thirty-three articles were included which made up a total of four RCTs. Two open-label studies compared deferasirox to placebo or standard therapy of deferoxamine. One phase II and phase III study compared deferasirox to standard treatment with deferoxamine. The quality of each study was assessed utilizing the Risk of Bias Tool evaluation following the recommendations from the Cochrane collaboration and the evidence was evaluated using the GRADE assessment tool. The characteristics of the patients in the original studies were fully outlined. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. Risk of bias was stated to be high for both studies since they were classified as open-label trials. Since only four studies were used in the review, funnel plots were not used to assess publication bias. Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. Risk of bias was determined to be “unclear” in all included studies. No deaths were observed during the two studies comparing deferasirox to placebo. Since the two studies were dose-finding studies focusing on pharmacokinetics or dynamics, efficacy was not a concentration so assessing of the end-points was not appropriate, although the studies met the inclusion criteria. For the two studies comparing deferasirox to deferoxamine, no significant difference in mortality was observed. No data on the outcomes of measures of iron excretion, reduced end-organ damage due to iron deposition, or cost were available. No significant differences were found in total adverse events. In one study, a subgroup analysis showed deferoxamine was significantly more effective than deferasirox in changing LIC and iron excretion-intake in highly iron-

overloaded patients by a mean ratio of 1.8:1. Participant satisfaction with treatment, convenience, and likelihood to continue therapy were significantly higher in deferasirox patients who had previously been treated with deferoxamine, but were not statistically significant in the small group of deferoxamine-naïve patients. Time lost from normal activities due to treatment was reported as being significantly less with deferasirox. The authors concluded that there is no evidence deeming deferasirox to be more superior to deferoxamine at the usually recommended ratio of 1 mg of deferasirox to 2 mg of deferoxamine but that similar efficacy may be achieved depending on dose and ratio. Data are limited and more long-term studies on efficacy and safety are needed.[5]

A systematic review of RCTs which evaluated the effectiveness (dose and method of administration) of desferrioxamine (also known as deferoxamine) in patients with transfusion-dependent thalasaemia was assessed.[6] The primary outcome assessed was mortality. Secondary outcomes included evidence of end-organ damage, measures of iron overload, adverse events or toxicity, participant adherence, and cost of intervention per year. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated. One author screened all titles and abstracts of identified papers for relevance and two authors independently screened full papers and identified relevant studies for inclusion. Disagreement was resolved via consensus or through a third party. A list of included studies was provided, although a list of excluded studies could not be found. One-hundred thirty-four full-text articles were assessed for eligibility. Eighty-three were excluded. Twenty-two studies were included in the qualitative synthesis, nine of which were listed as being relevant. Various comparisons were made, including desferrioxamine versus deferiprone or deferasirox; desferrioxamine and deferiprone versus deferiprone; or desferrioxamine monotherapy; different routes of desferrioxamine administration were also assessed. The quality of each study was assessed utilizing the Risk of Bias Tool evaluation following the recommendations from the Cochrane collaboration and the evidence was evaluated using the GRADE assessment tool. The characteristics of the patients in the original studies were fully outlined. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. In general, risk of bias was stated to be unclear. Funnel plots were not used to assess publication bias. Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. One trial reported mortality as an outcome, which noted one death occurred in the deferiprone treatment group after six months of treatment but was determined not to be due to treatment. At 12 months, meta-analysis from the results of three trials showed a significant change in LVEF in favor of deferiprone (MD -1.60%, 95% CI -2.97 to -0.24), although heterogeneity was observed to be high (I^2=75%). Two trials showed a significant difference in mean change in serum ferritin from baseline at six months in patients taking desferrioxamine (MD -2108.62 ng/mL, 95% CI -3334.48 to -882.76; and 324.20 ng/mL, 95% CI -1156.81 to 1805.21), but no significant difference at 12 or 24 months. Significant differences in mean urinary iron excretion was seen in two trials favoring deferiprone in one trial and desferrioxamine in the other (MD -0.20 mg/24 hr, 95% CI -0.32 to -0.08; MD 4.10 mg/24 hr, 95% CI 0.08 to 8.12; respectively). LIC was higher in patients taking desferrioxamine versus deferiprone after 12 months according to results from three trials (ratio of geometric means 1.49, 95% CI 1.06 to 2.09), after 24 months in one trial (1.45, 95%CI 0.90 to 1.80), after 30 and 34 months in two trials with one reaching significant difference (0.51, 95%CI 0.36 to 0.71). The geometric mean value of myocardial T2 in one trial in patient receiving desferrioxamine was 10% lower than in patients receiving deferiprone after six months (0.92, 95% CI 0.85 to 0.99) and 12 months (0.90, 95% CI 0.82 to 0.98). One trial reported mean chelation efficiency as [iron excretion (mg/kg/day/chelator dose (mg/kg/day)[x [molecular weight of the respective chelator/56] x n x 100 where 56 is the molecular weight of iron and n=3 with deferiprone and n=1 with desferrioxamine. A statistically significant difference was found in favor of desferrioxamine (16.45%, 95% CI 7.05 to 25.85). One trial reported data showing patients receiving desferrioxamine have a lower risk of experiencing an adverse event compared to those taking deferiprone (RR 0.45, 95%CI 0.24 to 0.84). One trial at three years showed a significant difference in participant adherence in favor or deferiprone (MD -23.30%, 95% CI -25.08 to -21.52). Based on the results, the authors recommended desferrioxamine as first-line therapy for iron overload in patients with thalassemia major and deferiprone or deferasirox in patients whom desferrioxamine is inadequate or contraindicated. More adequately-powered, high-quality, trials comparing long-term efficacy and outcomes are needed.[6]

New Guidelines:
None identified.

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New Safety Alerts:
Exjade®: In October 2013, the FDA added warnings and precautions were added regarding the post-marketing findings of Stevens-Johnson Syndrome.[7] In September 2012, a black boxed warning, contraindications, warning and precautions, and adverse reactions sections were revised in include risk for tubulointerstitial nephritis, hepatic failure, and gastrointestinal hemorrhage.[7]

New Formulations or Indications:
Jadenu™ is a tablet formulation of deferasirox approved by the FDA March 2015 for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis in patients 2 years of age and older and for the treatment of chronic iron overload in patients 10 years of age and older with nontrasfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 mg of iron per gram of liver dry weight (mg fe/g dw) and a serum ferritin greater than 300 mcg/L.[8] No specific clinical data for Jadenu™ was assessed because clinical safety and efficacy data for Exjade® (deferasirox), a tablet formulation for oral suspension, was previously reviewed by the FDA.[9]

Randomized Controlled Trials:

A total of 118 potentially relevant citations were evaluated from the literature search. After further review, most were excluded because of observational design or inappropriate control (placebo or no control). The remaining 4 randomized clinical trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Calvaruso G.[10] MC, RCT, OL	1. DFP PO 25 mg/kg TID 7 days/week 2. DFO SC 50 mg/kg/day 5 days/week	Age >13 years w/ sickle-cell-disease and serum ferritin 800-3000 ng/mL	Change from baseline value in serum ferritin levels during the 5 years (mean ± SD)	DFP: 695.00 ± 597.74 DFO: 1333.85 ± 871.74
Calvaruso G.[11] MC, RCT, OL	1. DFP PO 25 mg/kg TID 7 days/week 2. DFO SC 50 mg/kg/day 5 days/week	Age >13 years w/ thalassemia intermedia and serum ferritin 800-3000 ng/mL	Mean change in serum ferritin level over the 5-year period	No significant difference
Vichinsky E.[12] MC, RCT, OL	1. DFS PO 20 mg/kg/day 2. DFO SC 175 mg/kg/week	Age ≥2 years with sickle-cell-disease and having received ≥120 mL/kg of packed red blood cells or equivalent, or if LIC ≥7 mg Fe/g dry weight, serum ferritin levels ≥1000 ng/mL and body weight ≥10 kg	Safety during 24 weeks	Adverse events DFS: 110/125 (81.5%) DFO: 52/56 (92.9%)
Pennell D.J.[13] MC, RCT, OL	1. DFS PO 40 mg/kg/day 2. DFO SC 50-60 mg/kg/day 5-7 days/week	Age ≥10 years with β-thalassemia major, Diamond-Blackfan anemia, low/intermediate 1	Ratio of the geometric mean Gmean T2* after 1 year of treatment with DFS divided by the ratio of Gmean for DFO (95% CI)	1.055 (0.999 to 1.129) P=0.054

		myelodysplastic syndromes, or sideroblastic anemia with myocardial T2* 6 to 20 milliseconds without clinical symptoms of cardiac dysfunction		

Abbreviations: DFO = deferoxamine; DFP = deferiprone; DFS = deferasirox; Gmean = geometric mean; kg = kilograms; MC = multi-centered; mg = milligrams; mL = milliliters; ng = nanograms; OL = open label; PO = orally; RCT = randomized controlled trial; SC = subcutaneously; SD = standard deviation; TID = three times daily.

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11. Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus deferoxamine in thalassemia intermedia: results from a 5-year long-term Italian multicenter randomized clinical trial. *American Journal of Hematology*. 2015; 90(7): 634-638.\

12. Vichinsky E, Torres M, Minniti CP, et al. Efficacy and safety of deferasirox compared with deferoxamine in sickle cell disease: Two-year results including pharmacokinetics and concomitant hydroxyurea. *Am. J. Hematology*. 2013; 88:1068-1073.

13. Pennell DJ, Porter JB, Piga A, et al. A 1-year randomized controlled trial of deferasirox vs deferoxamine for myocardial iron removal in β-thalassemia major (CORDELIA). *Blood*. 2014; 123(10): 1447-1454.

Appendix 1: Current Status on Preferred Drug List

Form	Brand	Generic	PDL
VIAL	DEFEROXAMINE MESYLATE	DEFEROXAMINE MESYLATE	Y
VIAL	DESFERAL MESYLATE	DEFEROXAMINE MESYLATE	Y
VIAL	DEFEROXAMINE MESYLATE	DEFEROXAMINE MESYLATE	Y
VIAL	DESFERAL	DEFEROXAMINE MESYLATE	Y
TABLET	FERRIPROX	DEFERIPRONE	N
TAB DISPER	EXJADE	DEFERASIROX	N
TAB DISPER	EXJADE	DEFERASIROX	N
TAB DISPER	EXJADE	DEFERASIROX	N
TABLET	JADENU	DEFERASIROX	N
TABLET	JADENU	DEFERASIROX	N
TABLET	JADENU	DEFERASIROX	N

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Date: January 2016

Appendix 2: Abstracts of Clinical Trials

Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus Deferoxamine in Sickle Cell Disease: Results from a 5-year long-term Italian multi-center randomized clinical trial. *Blood Cells, Molecules and Diseases*. 2014; 53: 265–271.

Blood transfusion and iron chelation currently represent a supportive therapy to manage anemia, vasculopathy and vaso-occlusion crises in Sickle-Cell-Disease. Here we describe the first 5-year long-term randomized clinical trial comparing deferiprone versus deferoxamine in patients with Sickle Cell Disease. The results of this study show that deferiprone has the same effectiveness as deferoxamine in decreasing body iron burden, measured as repeated measurements of serum ferritin concentrations on the same patient over 5 years and analyzed according to the linear mixed-effects model (LMM) (p=0.822).
Both chelators are able to decrease, significantly, serum ferritin concentrations, during 5 years, without any effect on safety (p=0.005). Moreover, although the basal serum ferritin levels were higher in transfused compared with non-transfused group (p=0.031), the changes over time in serum ferritin levels were not statistically significantly different between transfused and non-transfused cohort of patients (p=0.389).
Kaplan–Meier curve, during 5 years of study, suggests that deferiprone does not alter survival in comparison with deferoxamine (p=0.38).
In conclusion, long-term iron chelation therapy with deferiprone was associated with efficacy and safety similar to that of deferoxamine. Therefore, in patients with Sickle Cell Disease, deferiprone may represent an effective long-term treatment option.

Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus deferoxamine in thalassemia intermedia: results from a 5-year long-term Italian multicenter randomized clinical trial. *Am J Hematol*. 2015; 90:634-638.

In patients with thalassemia intermedia (TI), such as beta-TI, alpha-thalassemia (mainly HbH disease and mild/moderate forms of HbE/beta-thalassemia), iron overload is an important challenge in terms of diagnosis, monitoring, and treatment. Moreover, to date, the only possible chelators available are deferoxamine, deferasirox, and deferiprone. Here, we report the first 5-year long-term randomized clinical trial comparing the effectiveness of deferiprone versus deferoxamine in patients with TI. Body iron burden, which was determined by measuring serum ferritin levels in the same patient over 5 years and analyzed according to the generalized linear mixed model (GLMM), showed a linear decrease over time in the mean serum ferritin levels in both treatment groups (P=0.035). The overall period of observation was 235.2 person-years for the deferiprone patients compared with 214.3 person-years for the deferoxamine patients. The results of the log-rank test suggested that the deferiprone treatment did not affect survival compared with the deferoxamine treatment (P=0.360). The major adverse events observed included gastrointestinal symptoms and joint pain or arthralgia. Neutropenia and agranulocytosis were also detected, suggesting needing of strict hematological control. In conclusion, long-term iron chelation therapy with deferiprone is associated with an efficacy and safety similar to that of deferoxamine, suggesting that this drug is an alternative option in cases in which deferoxamine and deferasirox are contraindicated.

Vichinsky E, Torres M, Minniti CP, et al. Efficacy and safety of deferasirox compared with deferoxamine in sickle cell disease: Two-year results including pharmacokinetics and concomitant hydroxyurea. *Am J Hematol*. 2013; 88:1068-1073.

We report a prospective, randomized, Phase II study of deferasirox and deferoxamine (DFO) in sickle cell disease patients with transfusional iron overload, with all patients continuing on deferasirox after 24 weeks, for up to 2 years. The primary objective was to evaluate deferasirox safety compared with DFO; long-term efficacy and safety of deferasirox was also assessed. We also report, for the first time, the safety and pharmacokinetics of deferasirox in patients concomitantly receiving hydroxyurea. Deferasirox (n=5135) and DFO (n=568) had comparable safety profiles over 24 weeks. Adverse events (AEs) secondary to drug administration were reported in 26.7% of patients in the deferasirox cohort and 28.6% in the DFO cohort. Gastrointestinal disorders were more common with

deferasirox, including diarrhea (10.4% versus 3.6%) and nausea (5.2% versus 3.6%). The most common AE in the DFO group was injection-site pain irritation, which occurred in 7% of patients. Acute renal failure occurred in one patient on deferasirox who was continued on medication despite progressive impairment of renal function parameters. Serum ferritin levels were reduced in both treatment groups. Patients continuing on deferasirox for up to 2 years demonstrated an absolute median serum ferritin decrease of 2614 ng/mL (n=596). Increasing deferasirox dose was associated with improved response and a continued manageable safety profile. Concomitant hydroxyurea administration (n=528) did not appear to influence the efficacy, safety (including liver and kidney function), and pharmacokinetic parameters of deferasirox.

Pennell DJ, Porter JB, Piga A, et al. A 1-year randomized controlled trial of deferasirox vs deferoxamine for myocardial iron removal in b-thalassemia major (CORDELIA). *Blood*. 2014; 123:1447-1454.

Randomized comparison data on the efficacy and safety of deferasirox for myocardial iron removal in transfusion dependent patients are lacking. CORDELIA was a prospective, randomized comparison of deferasirox (target dose 40 mg/kg per day) vs subcutaneous deferoxamine (50-60 mg/kg per day for 5-7 days/week) for myocardial iron removal in 197 b-thalassemia major patients with myocardial siderosis (T2* 6-20 milliseconds) and no signs of cardiac dysfunction (mean age, 19.8 years). Primary objective was to demonstrate non-inferiority of deferasirox for myocardial iron removal, assessed by changes in myocardial T2* after 1 year using a per-protocol analysis. Geometric mean (Gmean) myocardial T2* improved with deferasirox from 11.2 milliseconds at baseline to 12.6 milliseconds at 1 year (Gmeans ratio, 1.12) and with deferoxamine (11.6 milliseconds to 12.3 milliseconds; Gmeans ratio, 1.07). The between-arm Gmeans ratio was 1.056 (95% confidence interval [CI], 0.998, 1.133). The lower 95% CI boundary was greater than the pre-specified margin of 0.9, establishing non-inferiority of deferasirox vs deferoxamine (P=0.057 for superiority of deferasirox). Left ventricular ejection fraction remained stable in both arms. Frequency of drug-related adverse events was comparable between deferasirox (35.4%) and deferoxamine (30.8%). CORDELIA demonstrated the noninferiority of deferasirox compared with deferoxamine for myocardial iron removal.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to September Week 1 2015
1 deferasirox.mp. 619
2 deferoxamine.mp. or exp Deferoxamine/ 3494
3 deferiprone.mp. 745
4 1 or 2 or 3 4193
5 limit 4 to (english language and yr="2012 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 118

Author: J. Lee, Pharm.D. Date: January 2016