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HEALTH TECHNOLOGY BRIEFING DECEMBER 2020

Deferiprone for transfusional iron overload in sickle cell disease and other anaemias – First Line

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Developer/Company	Chiesi Ltd	**UKPS ID**	658433

Licensing and market availability plans	In phase III clinical trials

SUMMARY

Deferiprone is in clinical development for patients with sickle-cell disorder (SCD) and other anaemias that are suffering from iron overload due to frequent transfusions to increase their red blood cell count. SCD is a group of inherited disorders where the red blood cells become hard and sticky and look like a C-shaped farm tool called a "sickle". The sickle red blood cells die early, and patients often require blood transfusions. Iron overload is an effect of frequent transfusions in SCD. Excess iron in the body can be toxic to major organs like the heart and liver

Deferiprone is administered orally and can reduce iron overload by binding to it, forming a complex, which can then be excreted in the urine. This reduces iron levels in the body, preventing iron toxicity. If licensed, deferiprone would offer an additional first-line treatment for transfusional iron overload in sickle-cell disease and other anaemias.

PROPOSED INDICATION

Patients aged 2 years and older with transfusional iron overload due to sickle cell disease or other anaemias.[1]

TECHNOLOGY

DESCRIPTION

Deferiprone (Ferriprox) is chelating agent, with a high affinity for iron. It binds iron in a 3:1 molar ratio (deferiprone: iron), forming a stable complex which is then eliminated mainly in the urine.[2] Deferiprone has a lower binding affinity for other metals such as copper, aluminium and zinc than for iron.[3]

Deferiprone is in clinical development for the treatment of transfusional iron overload in patients with sickle cell disease or other anaemias (2013-002181-39, 2014-005685-30). Deferiprone is usually given as 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to 100 mg/kg body weight. Dose per kilogram body weight should be calculated to the nearest half tablet or to the nearest 2.5 mL volume of oral solution.[2]

INNOVATION AND/OR ADVANTAGES

This is a new indication for deferiprone; data for the use in children under 6 have not been shown before.[2] Very few drugs are used daily at the high doses of deferiprone and have such low toxicity.[4]

There are currently two other chelating agents that are licensed for use in sickle cell disease (SCD) but these have significant side effects.[5] Deferiprone would offer an alternative to these treatments.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The European Medicines Agency granted Orphan Drug Designation to deferiprone for the treatment of sickle cell disease in 2011.[6]

Deferiprone is currently licensed in the UK for the following indications:[2]

- As a monotherapy for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.
- In combination with another chelator, in patients with thalassaemia major, when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.

Deferiprone is currently in phase II/III trials for amyotrophic lateral sclerosis, dementia, brain aneurysms and beta-thalassemia.[7]

The most common side effects (≥1/10 cases) are nausea, abdominal pain, vomiting and chromaturia.[2]

PATIENT GROUP

DISEASE BACKGROUND

Sickle cell disease (SCD) is an inherited chronic haemolytic anaemia that results from a single amino acid substitution in the β-globin chain, producing the abnormal haemoglobin-S (HbS). Blood transfusion plays a prominent role in the management of patients with SCD, but causes significant iron overload.[8] The human body has no effective physiological mechanism for excreting excess iron. Therefore, in conditions such as SCD, where transfusions are frequently indicated, exogenous iron can accumulate, circulate as nontransferrin bound iron (NTBI), enter tissues, form reactive oxygen species (ROS), and result in end organ damage. However, patients with SCD, compared with thalassemic patients, despite a similar transfusion load, may be relatively protected from iron mediated cardiac and endocrine gland toxicity.[9]

Blood transfusion in SCD has been shown to lead to iron deposition within the liver predominantly (and therefore is associated with liver damage, fibrosis, cirrhosis and possible liver failure) but also extra hepatic organs. There is less robust evidence regarding chelation in sickle cell disease compared to thalassaemia but the aim of chelation is to reduce the risk of complications of iron overload, which may develop with intermittent or regular transfusions.[8]

Symptoms of iron overload include tiredness or weakness, loss of sex drive, weight loss, abdominal pain, joint aches or pain, gray-colored or bronze-colored skin, shortness of breath, arthritis, liver disease, including cirrhosis or liver cancer, enlarged spleen that may cause abdominal pain or difficulty eating a normal-sized meal, diabetes, shrunken testicles and heart problems, including both heart failure and heart rhythm problems.[10]

CLINICAL NEED AND BURDEN OF DISEASE

SCD is estimated to affect 1 in every 2000 live births in England, and it is now the most common genetic condition at birth. It is estimated that about 350 babies are born each year in England with sickle cell disease and a further 9500 babies are found to be carriers of the disease. There are more than 12,500 people with sickle cell disease in England, and about 240,000 are carriers. The highest prevalence of sickle cell disease is among Black African and Black Caribbean people, but cases also occur in families originating from the Middle East, parts of India, the eastern Mediterranean, and South and Central America; the common factor to this geographical distribution is a history of malaria, or migration from a malarial area. Due to population migration, however, sickle cell disease is an important part of clinical practice in most countries.[11]

Life expectancy of those with SCD has improved considerably over the last decades, due to improvements in the management of infections and other complications in childhood; new interventions; active health maintenance for adults and counselling. It is estimated that more than 90% of people of all phenotypes will survive past 20 years of age, and significant numbers are older than 50 years of age.[12]

Given that blood transfusions are offered in both acute and chronic complications with SCD, it can be assumed that many SCD patients will have a transfusion within their life and therefore, could be susceptible to iron overload.[5,13]

In 2019-2020 in the UK there were 27,924 hospital admissions with a primary diagnosis of sickle-cell disorders (ICD-10 code D57), 33,033 finished consultant episodes and 46,631 bed days.[14]

In 2019-2020 in the UK there were 76,689 hospital admissions with a primary diagnosis of disorders of iron metabolism (ICD-10 code E83.1), 76,750 finished consultant episodes and 1,047 FCE bed days.[14]

The company estimates less then 1 per 50,000 will be eligible for treatment.[a]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aim of chelation is to reduce the risk of complications of iron overload, which may develop with intermittent or regular blood transfusions. The following are recommended for SCD patients undergoing transfusions:[5]

- All patients with serum ferritin persistently raised >1000 µg/l who have been previously transfused should have quantitative monitoring of liver iron concentration using magnetic resonance imaging (MRI).
- Iron chelation is recommended in patients who have a liver iron concentration of > 7mg/g dry weight on MRI scanning.
- Patients receiving long term blood transfusion should have regular monitoring for iron overload and appropriate iron chelation therapy according to their iron burden.
- All patients receiving iron chelation therapy should be regularly monitored for therapeutic effect and chelator toxicity.
- Support should be provided to patients to help improve adherence to chelation therapy

CURRENT TREATMENT OPTIONS

Iron chelators that are currently licensed in the EU/UK are:[5]

- Deferasirox
- Desferrioxamine

PLACE OF TECHNOLOGY

If licensed, deferiprone will offer a first-line treatment for patients with SCD suffering from iron overload.

CLINICAL TRIAL INFORMATION

Trial	**FIRST**; NCT02041299; 2013-002181-39; The Efficacy and Safety of Ferriprox® for the Treatment of Transfusional Iron Overload in Patients With Sickle Cell Disease or Other Anaemias **Phase IV** – prematurely ended	NCT02443545; 2014-005685-30; Long-term Safety and Efficacy Study of Ferriprox® for the Treatment of Transfusional Iron Overload in Patients With Sickle Cell Disease or Other Anaemias **Phase IV** - prematurely ended

[a] Information provided by Chiesi Ltd on UK PharmaScan

	Locations: US, Canada, EU (incl. UK) plus other locations	**Location(s):** US, Canada, UK, Egypt and Saudi Arabia
Trial design	Randomised, parallel assignment, open-label, active-controlled	Randomised, parallel assignment, open-label, active-controlled
Population	Aged 2 years or older; have sickle cell disease (confirmed by Hb electrophoresis or more specific tests) or other conditions with iron overload from repeated blood transfusions	Aged 3 years and older; completed study LA38-0411 (NCT02041299)
Intervention(s)	Deferiprone (oral) 3 times daily for 52 weeks	Deferiprone (oral) 3 times daily for 3 years
Comparator(s)	Deferoxamine (SC) given 5 to 7 days per week for 52 weeks	Patients in this group are those who were randomised to the deferoxamine arm in study LA38-0411, and hence received deferiprone for 2 years
Outcome(s)	Change in liver iron concentration, as measured in mg/g dry weight (dw) using MRI [Time Frame: Change from baseline to Week 52] See trial record for full list of other outcomes	• Number of subjects with adverse events (AEs) [Time Frame: From the first day of the study until the last study visit (Week 104 or early termination)] • Number of subjects with serious adverse events (SAEs) [Time Frame: From the first day of the study until 30 days after the last dose] • Discontinuations due to adverse events [Time Frame: From the first day of the study until Week 104] See trial record for full list of other outcomes
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

Ferriprox 500mg tablets have an NHS indicative price of £130.00.[15] Ferriprox 1000mg tablets have an NHS indicative price of £130.00.[15] Ferriprox 100mg/ml oral solution has a NHS indicative price of £152.39.[15]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE quality standard. Sickle cell disease (QS58). April 2014

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Services for Haemoglobinopathy Care (All Ages). B08/S/a

OTHER GUIDANCE

- Sickle Cell Society. Sickle Cell Disease in Childhood: Standards and Recommendations for Clinical Care. 2019.[16]
- Sickle Cell Society. Standards for the clinical care of adults with sickle cell disease in the UK. 2018.[5]
- NICE Clinical Knowledge Summary. Sickle cell disease. November 2016.[17]
- Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Journal of Haemotology. 2016.[18]
- Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. British Journal of Haemotology. 2016. [13]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *Efficacy and Safety of Ferriprox® in Patients With Sickle Cell Disease or Other Anemias (FIRST). Trial ID: NCT02041299*. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02041299?term=Deferiprone&cond=sickle&draw=2&rank=3 [Accessed 30 October 2020].

2 Electronic Medicines Compendium (eMC). *Ferriprox 500 mg film-coated tablets.* 2020. Available from: https://www.medicines.org.uk/emc/product/10908/smpc [Accessed 30 October 2020].

3 FDA. *FERRIPROX® (deferiprone) tablets, for oral use.* 2011. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021825lbl.pdf [Accessed 30 October 2020].

4 Kontoghiorghes G, Neocleous K, Kolnagou A. Benefits and Risks of Deferiprone in Iron Overload in Thalassaemia and Other Conditions. *Drug Safety*. 2003;26(8):553-84. Available from: https://doi.org/10.2165/00002018-200326080-00003.

5 Sickle Cell Society. *Standards for Clinical Care of Adults with Sickle Cell Disease in the UK.* 2018. Available from: https://www.sicklecellsociety.org/wp-content/uploads/2018/05/Standards-for-the-Clinical-Care-of-Adults-with-Sickle-Cell-in-the-UK-2018.pdf [Accessed 30 October 2020].

6 European Medicines Agency (EMA). *EU/3/10/832* 2011. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu310832 [Accessed 30 October 2020].

7 ClinicalTrials.gov. *37 Studies found for: Deferiprone | Phase 2, 3.* 2020. Available from: https://clinicaltrials.gov/ct2/results?term=Deferiprone&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 30 October 2020].

8 Coates T, Wood J. How we manage iron overload in sickle cell patients. *British Journal of Haemotology*. 2017;177(5):703-16. Available from: https://doi.org/https://dx.doi.org/10.1111%2Fbjh.14575.

9 Raghupathy R, Manwani D, Little JA. Iron Overload in Sickle Cell Disease. *Advances in Hematology*. 2010 2010/05/17;2010:272940. Available from: https://doi.org/10.1155/2010/272940.

10 AAMDS. *Iron Chelation.* Available from: https://www.aamds.org/treatments/therapies/iron-chelation [Accessed 9 November 2020].
11 National Insitute for Health and Care Excellence. *How common is sickle cell disease?* 2016. Available from: https://cks.nice.org.uk/topics/sickle-cell-disease/background-information/prevalence/ [Accessed 9 November 2020].
12 National Insitute for Health and Care Excellence. *What is the prognosis?* Available from: https://cks.nice.org.uk/topics/sickle-cell-disease/background-information/prognosis/ [Accessed 13 November 2020].
13 Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. *British journal of haematology*. 2017;176(2):192-209. Available from: https://doi.org/https://doi.org/10.1111/bjh.14383.
14 NHS Digital. *Hospital Admitted Patient Care Activity, 2019-20: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20
15 British National Formulary (BNF). *DEFERIPRONE*. Available from: https://bnf.nice.org.uk/medicinal-forms/deferiprone.html [Accessed 30 October 2020].
16 Sickle Cell Society. *Sickle Cell Disease in Childhood: Standards and Recommendations for Clinical Care.* 2019. Available from: https://www.sicklecellsociety.org/wp-content/uploads/2019/11/SCD-in-Childhood_Final-version-1.pdf [Accessed 30 October 2020].
17 National Insitute for Health and Care Excellence (NICE). *Sickle cell disease.* 2016. Available from: https://cks.nice.org.uk/topics/sickle-cell-disease/ [Accessed 30 October 2020].
18 Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. *British journal of haematology*. 2017;176(2):179-91. Available from: https://doi.org/https://doi.org/10.1111/bjh.14346.

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