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HEALTH TECHNOLOGY BRIEFING
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Vadadustat for treating anaemia in chronic kidney disease

NIHRIO ID	15115	**NICE ID**	10093
Developer/Company	Otsuka Pharmaceutical UK Ltd	**UKPS ID**	645985

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Vadadustat is in development for the treatment of anaemia in patients with chronic kidney disease (CKD). Anaemia is a condition where the body has fewer red blood cells (RBC) to carry oxygen throughout the body resulting in a decline in function of the body's organs and tissues. Symptoms of anaemia in CKD patients include weakness, fatigue, headaches, dizziness and difficulty breathing. Anaemia is common in people with CKD because diseased kidneys produce less erythropoietin (EPO) which is needed to make RBCs. Current treatment for anaemia in CKD involves erythropoietin stimulating agents (ESAs) however, they may result in adverse side-effects so there is a need for safer treatment options.

Vadadustat, (given orally), works by stimulating the pathways that result in more RBC being produced under low oxygen conditions. Under low oxygen conditions, key regulatory proteins known as hypoxia inducible factors (HIFs) activate genes involved in RBC production to increase the number or RBC available in the blood. If licenced, vadadustat will offer an additional treatment option for anaemia in patients with CKD.

PROPOSED INDICATION

Correction and maintenance treatment of anaemia in patients with dialysis dependent chronic kidney disease (DD-CKD) and non-dialysis dependent chronic kidney disease (NDD-CKD).[1-4]

TECHNOLOGY

DESCRIPTION

Vadadustat (AKB-6548) belongs to the class of organic compounds known as n-acyl-alpha amino acids. These are compounds containing an alpha amino acid which bears an acyl group at its terminal nitrogen atom.[5] Vadadustat is a titratable, oral, hypoxia inducible factor prolyl hydroxylase (HIF-PH) enzyme inhibitor. It stimulates the hypoxia response pathway by stabilizing key regulatory proteins called HIFs. Under normal conditions when sufficient oxygen is present, HIF proteins are targeted for degradation by HIF-PH to maintain homeostasis in red blood cell (RBC) production. Under hypoxic conditions, HIF-PH activity is reduced resulting in stabilisation of HIFs and activation of HIF signalling. Stable HIFs move to the nucleus resulting in transcriptional activation of target genes that increase erythropoietin (EPO) synthesis and iron metabolism.[5,6] HIF-PH inhibitors like vadadustat are a promising new class of drugs that activate HIF signalling, increasing endogenous EPO production and stimulating iron metabolism.[6]

Vadadustat is currently in phase III clinical development for the treatment of anaemia in patients with CKD. In the trials PRO$_2$TECT (NCT02648347, EudraCT 2015-004265-81); PRO$_2$TECT-CONVERSION (NCT02680574, EudraCT 2015-004774-14); INNO$_2$VATE (NCT02865850, EudraCT 2016-000838-21); INNO$_2$VATE-CORRECTION (NCT02892149, EudraCT 2016-001360-11) patients are given an oral tablet of vadadustat once daily and the dose is adjusted compared to their Hb level.[1-4,]

INNOVATION AND/OR ADVANTAGES

Current standard care for treating anaemia in CKD involves the use of injectable erythropoiesis stimulating agents (ESA). While ESAs have been shown to be effective in treating anaemia, they can lead to substantial haemoglobin oscillations above the target range and high levels of circulating erythropoietin.[6,7]

Therefore there is a need for alternative treatments that limit the erythropoietin exposure.[7] Vadadustat uses a different mechanism of action to ESAs and results from the phase III INNO$_2$VATE (NCT02865850) study showed that vadadustat met the primary safety and efficacy endpoints for the treatment of anaemia in patients with dialysis dependent chronic kidney disease.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Vadadustat does not currently have Marketing Authorisation in the EU/UK for any indication.

Vadadustat is also in phase II clinical development for the treatment of acute respiratory distress syndrome in hospitalised patients with Covid-19.[9]

PATIENT GROUP

DISEASE BACKGROUND

Anaemia is a condition in which the body has fewer RBC than normal. RBC contain haemoglobin which carries oxygen throughout the body to tissues and organs. In people with anaemia there is a reduced ability to carry oxygen so the tissues and organs may not function as well as they should.[10,11] The World Health Organisation defines anaemia as a reduction in the number of RBC that results in a haemoglobin concentration <13.0g/dL for adult males and postmenopausal women and <12.0g/dL for premenopausal women.[12] EPO is a hormone produced in the stromal cells near the proximal tubule of the kidney which helps the body to make RBC.[13] Anaemia commonly occurs in people with CKD because when the kidneys are diseased or damaged they do not make sufficient amounts of EPO so there is a reduced production of RBC.[10,13]

In a small proportion of people with CKD, the kidneys will eventually stop working and they may require dialysis to perform the job of filtering the blood and removing waste products that healthy kidneys normally perform.[14-16] CKD patients who undergo haemodialysis treatment lose an additional 1-2g of iron per year through frequent blood drawing for laboratory tests and surgical procedures for vascular access machine or because their dialysis diet does not contain enough sources of iron rich foods.[17,18] Most patients with stage 5 CKD requiring dialysis have anaemia which contributes to poor quality of life and outcomes in these patients.[19]

The signs and symptoms of anaemia in someone with CKD may include: weakness, fatigue, headaches, problems with concentration, paleness, dizziness, difficulty breathing, pale complexion, trouble sleeping or chest pain.[10,11] Complications of anaemia in someone with CKD include: heart problems, such as an irregular heartbeat or an unusually fast heartbeat, especially when exercising and the harmful enlargement of muscles in the heart. In addition, heart failure can also occur whereby the heart can't pump enough blood to meet the body's needs.[10] Age, sex and ethnicity are important risk factors for the development of anaemia in CKD patients.[12,20] There is a greater prevalence of anaemia amongst females, African-Americans and those aged over 75 years.[20,21]

CLINICAL NEED AND BURDEN OF DISEASE

Based on world health organisation (WHO) anaemia diagnostic criteria nearly 90% of patients with a glomerular filtration rate (GFR) <25 to 30 mL/min, which would be classed as stage 4 or 5 CKD, have anaemia.[12,15]

In England in 2019-20 there were 51,206 finished consultant episodes (FCE) for CKD stage 4 and 5 (ICD-10 code N18.4 and N18.5) resulting in 35,467 admissions, 20,025 day cases and 108,494 FCE bed days.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Diagnostic evaluation of anaemia in CKD should include the following tests:[20]

- percentage of hypochromic RBC
- reticulocyte haemoglobin content
- combination transferrin saturation measurement and serum ferritin measurement
- haemoglobin levels

The first step in treating anaemia is raising low iron levels. A dietitian can help patients choose foods that are a good source of iron and supplemental iron can be given to patients either intravenously or in the form of iron pills.[10,17] Patients are also offered treatment with ESAs to keep haemoglobin levels within the aspirational range of 10.0g/dL and 12.0g/dL.[20]

Haemoglobin levels should be assessed regularly to assess if anaemia treatment is working.[17]

CURRENT TREATMENT OPTIONS

For treating anaemia in people with CKD, NICE recommends the following:[20]

- Iron supplementation
- ESA

PLACE OF TECHNOLOGY

If licensed, vadadustat will offer an additional treatment option for anaemia in patients with CKD.

CLINICAL TRIAL INFORMATION

Trial	**INNO$_2$VATE-CONVERSION, NCT02892149, EudraCT 2016-001360-11; Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anaemia in Subjects With Dialysis-Dependent Chronic Kidney Disease (DD-CKD)** **Phase III - Completed** **Location(s): 7 EU countries (incl UK) USA, Canada and other countries** **Primary completion date: 16 January 2020**
Trial design	Randomized, Open-label, Active-Controlled
Population	N=3554; adults aged over 18 years of age; receiving chronic maintenance dialysis for end-stage kidney disease for at

	least 12 weeks; currently maintained on ESA therapy; mean screening haemoglobin between 8.0 and 11.0g/dL in the US and between 9.0 and 12.0g/dL outside of the US
Intervention(s)	Vadadustat (oral tablet)
Comparator(s)	Darbepoetin alfa (intravenous or subcutaneous administration)
Outcome(s)	• Mean change in haemoglobin between baseline and the primary evaluation period [Time frame: Baseline visit, week 36] • Major adverse cardiovascular events (MACE), defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke [Time frame: from Baseline visit to end of study, minimum 1 year] See trial record for full list of outcome measures
Results (efficacy)	Vadadustat was non-inferior to darbepoetin alfa. The least square mean difference in Hb was -0.17 g/dL, achieving the pre-specified non-inferiority criterion of -0.75 g/dL. The mean (SD) Hb level at week 24 to week 36 was 10.36 (1.01) g/dL. Vadadustat sustained efficacy demonstrating non-inferiority to darbepoetin with a least square mean difference in Hb of -0.18 g/dL. The mean (SD) Hb level at week 40 to week 52 was 10.40 (1.04) g/dL in the vadadustat-treated patients compared to 10.58 (0.98) g/dL for darbepoetin treated patients.[8]
Results (safety)	The incidence of treatment emergent adverse events in the vadadustat treated patients was 88.3% and 89.3% in darbepoetin alfa treated patients. The most common treatment emergent adverse events reported in vadadustat/darbepoetin alfa treated patients were diarrhoea (13.0%/10.8%), pneumonia (11.0%/9.7%), hypertension (10.6%/13.8%), and hyperkalaemia (9.0%/10.8%). Serious treatment emergent adverse events were slightly lower for vadadustat treated patients at 55.0% and 58.3% for darbepoetin alfa-treated patients.[8]

Trial	**INNO$_2$VATE-CORRECTION/CONVERSIOIN, NCT02865850, EudraCT 2016-000838-21; Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction or Maintenance Treatment of Anaemia in subjects with Incident Dialysis Dependent Chronic Kidney Disease (DD-CKD)** **Phase III** - Completed **Location(s): 4 EU (not incl UK), USA and other countries** **Primary completion date:** 31 January 2020
Trial design	Randomized, Open-Label, Active-Controlled

Population	N=369; adults aged 18 years and older; initiated chronic maintenance dialysis (either peritoneal or haemodialysis) for end-stage kidney disease; mean screening haemoglobin between 8.0 and <11.0g/dL
Intervention(s)	Vadadustat (oral tablet)
Comparator(s)	Darbepoetin alfa (subcutaneous or intravenous administration)
Outcome(s)	• Mean change in haemoglobin between baseline and the primary evaluation period [Time Frame: Baseline visit, week 36] • MACE defined as all-cause mortality, non-fatal myocardial infarction or non-fatal stroke [Time frame: Baseline visit to end of study (event-driven, minimum 1 year)] See trial record for full list of outcome measures
Results (efficacy)	Vadadustat was non-inferior to darbepoetin alfa. The least square mean difference in Hb was -0.31 g/dL. The mean SD Hb level at week 24 to week 36 was 10.36 (1.13) g/dL for vadadustat-treated patients compared to 10.61 (0.94) g/dL for darbepoetin alfa-treated patients.[8]
Results (safety)	The incidence of treatment emergent adverse events in patients treated with vadadustat was 83.8% and 85.5% in the darbepoetin alfa treated patients. The most common treatment emergent adverse events reported in vadadustat/darbepoetin alfa treated patients were hypertension (16.2%/12.9%) and diarrhoea (10.1%/9.7%). Serious treatment emergent adverse events were lower in vadadustat treated patients at 49.7% compared to 56.5% for darbepoetin alfa treated patients.[23]

Trial	**PRO$_2$TECT-CONVERSION, NCT02680574, EudraCT 2015-004774-14; Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anaemia in Subjects With Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD)** **Phase III -** Completed **Location(s): 11EU countries (incl UK) USA, Canada and other countries** **Primary completion date: 18 June 2020**
Trial design	Randomized, Open-label, Active-Controlled
Population	N=1752; adults aged over 18 years of age; diagnosis of CKD with an eGFR ≤60mL/min/1.73m^2 at screening; not expected to start dialysis within 6 months of screening; currently maintained on ESA therapy; mean screening haemoglobin

	between 8.0 and 11.0g/dL in the US and between 9.0 and 12.0g/dL outside of the US
Intervention(s)	Vadadustat (oral tablet)
Comparator(s)	Darbepoetin alfa (intravenous or subcutaneous administration)
Outcome(s)	• Mean change in haemoglobin between baseline and the primary evaluation period [Time frame: Baseline visit, week 36] • MACE, defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke [Time frame: from Baseline visit to end of study, minimum 1 year] See trial record for full list of outcome measures
Results (efficacy)	Vadadustat was non-inferior to darbepoetin alfa. The least square mean difference in Hb was -0.01 g/dL, achieving the pre-specified non-inferior criterion of -0.75g/dL. The mean (SD) Hb level at week 24 to week 36 was 10.77 (0.98) g/dL for vadadustat treated patients compared to 10.77 (0.99) g/dL for darbepoetin alfa treated patients. Vadadustat sustained efficacy demonstrating non-inferiority to darbepoetin with a least square mean difference in H of 0.00 g/dL. The mean (SD) Hb level at week 40 to week 52 was 10.80 (1.04) g/dL in the vadadustat-treated patients compared to 10.79 (1.05) g/dL for darbepoetin alfa treated patients.[24]
Results (safety)	Vadadustat did not meet the PRO2TECT program's (Correction and Conversion studies n=3471) primary safety endpoint of non-inferiority for MACE. The upper bound of the 95% confidence interval of the hazard ratio (HR) was above the pre-specified NI margin of 1.25 for primary MACE analysis (HR 1.17, 95% CI: 1.01, 1.36). MACE is defined as the composite endpoint of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke. The incidence of treatment emergent adverse events during the Conversion study in vadadustat treated patients was 89.1% and 87.7% in darbepoetin alfa treated patients. The most common treatment emergent adverse events reported in vadadustat/darbepoetin alfa treated patients were end-stage renal disease (27.5%/28.4%), hypertension (14.4%/14.8%), urinary tract infection (12.2%/14.5%), diarrhoea (13.8%/8.8%), peripheral oedema (9.9%/10.1%) and pneumonia (10.0%/9.7%). Serious treatment emergent adverse events were 58.5% for vadadustat treated patients and 56.6% for darbepoetin alfa treated patients.[24]

Trial	**PRO$_2$TECT-CORRECTION, NCT02648347, EudraCT 2015-004265-81; Phase 3, Randomized, Open-Label, Active-**

	Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction Treatment of Anaemia in subjects with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) **Phase III -** Completed **Location(s): 7 EU (incl UK), USA, Canada and other countries** **Primary completion date: 04 June 2020**
Trial design	Randomized, Open-Label, Active-Controlled
Population	N=1761 adults aged 18 years and older; diagnosis of CKD with an eGFR <60mL/min/1.73m^2 at screening; not expected to start dialysis within 6 months of screening; mean screening haemoglobin <10.0g/dL
Intervention(s)	Vadadustat (oral tablet)
Comparator(s)	Darbepoetin alfa (subcutaneous or intravenous administration)
Outcome(s)	• Mean change in haemoglobin between baseline and the primary evaluation period [Time Frame: Baseline visit, Week 36] • MACE, defined as all-cause mortality, non-fatal myocardial infarction or non-fatal stroke [Time Frame: Baseline visit to end of study (event-driven, minimum 1 year)] See trial record for full list of outcome measures
Results (efficacy)	Vadadustat was non-inferior to darbepoetin alfa. The least square mean difference in Hb was 0.05 g/dL, achieving the pre-specified non-inferior criterion of -0.75 g/dL. The mean (SD) Hb level at week 24 to week 36 was 10.39 (0.99) g/dL for vadadustat-treated patients compared to 10.35 (1.03) g/dL for darbepoetin alfa-treated patients. Vadadustat sustained the target Hb efficacy response at weeks 40 to 52 achieving non-inferiority compared to darbepoetin alfa. The least square mean difference in Hb was 0.04 g/dL. The mean (SD) Hb level at week 40 to week 52 was 10.48 (1.05) g/dL. The mean (SD) Hb level at week 40 to week 52 was 10.48 (1.05) g/dL for vadadustat-treated patients compared to 10.45 (1.01) g/dL for darbepoetin alfa-treated patients.[24]
Results (safety)	Vadadustat did not meet the PRO2TECT program's (Correction and Conversion studies n=3471) primary safety endpoint of non-inferiority for MACE. The upper bound of the 95% confidence interval of the hazard ratio (HR) was above the pre-specified NI margin of 1.25 for primary MACE analysis (HR 1.17, 95% CI: 1.01, 1.36). MACE is defined as the composite endpoint of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke.

	The incidence of treatment emergent adverse events during the Correction study in the vadadustat treated patients was 90.9% and 91.6% in the darbepoetin alfa treated patients. The most common treatment emergent adverse events reported in vadadustat/darbepoetin alfa treated patients were end-stage renal disease (34.7%/35.2%), hypertension (17.7%/22.1%), hyperkalaemia (12.3%/15.6%), urinary tract infection (12.9%/12.0%), diarrhoea (13.9%/10.0%), peripheral oedema (12.5%/10.5%), fall (9.6%/10.0%) and nausea (10.0%/8.2%). Serious treatment emergent adverse events were 65.3% for vadadustat treated patients and 64.5% for darbepoetin treated patients.[24]

ESTIMATED COST

The estimated cost of vadadustat is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Roxadustat for treating anaemia in people with chronic kidney disease (ID1483). Expected publication date March 2022.
- NICE clinical guideline. Chronic kidney disease: managing anaemia (NG8). June 2016
- NICE clinical guideline. Renal replacement therapy and conservative management (NG107). October 2018.
- NICE clinical guideline. Chronic kidney disease in adults: assessment and management (CG182). January 2015.
- NICE quality standard. Chronic kidney disease in adults (QS5). July 2017.

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

- The Renal Association. Clinical Practice Guideline Anaemia of Chronic Kidney Disease. June 2017.[25]
- National Institute of Health and Care Excellence (NICE). Management of anaemia in chronic kidney disease: summary of updated NICE guidance. 2015.[26]
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ADDITIONAL INFORMATION

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