SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Vafseo 150 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vafseo 150 mg film-coated tablets
Each film-coated tablet contains 150 mg of vadadustat

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Vafseo 150 mg film-coated tablets
Round, white tablets debossed with “VDT” on one side and “150” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vafseo is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis.

4.2 Posology and method of administration

Posology

Dose initiation

The recommended starting dose is 300 mg once daily. Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently.

Patients converting from an erythropoiesis-stimulating agent (ESA)

When converting from an ESA to Vafseo, the recommended starting dose is 300 mg once daily,

Those patients converting from a high baseline dose of ESA may experience an initial decline in Hb levels before gradually returning to baseline Hb levels by Weeks 16 to 20 (see section 5.1 for course Hb during treatment in individual studies). Taking into account the gradual rise in Hb with Vafseo, rescue therapy in the form of red blood cell (RBC) transfusion or ESA treatment may be considered during the transition phase if Hb values fall below 9.0 g/dL or response is considered not acceptable (see section 4.4). Patients receiving RBC transfusions are recommended to continue Vafseo treatment during the transfusion period. Vafseo should be paused for those patients receiving temporary ESA rescue treatment and may be resumed when Hb levels are ≥10 g/dL. Depending on the ESA employed, the pause in Vafseo treatment should be extended to:

- 2 days after last dose of epoetin
- 7 days after last dose of darbepoetin alfa
- 14 days after last dose of methoxy polyethylene glycol-epoetin beta.

Following ESA rescue, Vafseo should be resumed at the prior dose or one dose higher, with subsequent titration according to the dose titration guidelines given below in this section.

Dose titration

When initiating or adjusting therapy, monitor Hb levels every two weeks until stable, then monitor at least monthly. Dose adjustment should be done in increments of 150 mg within the range of 150 mg to a maximum recommended daily dose of 600 mg to achieve or maintain Hb levels within 10 to 12 g/dL.

When adjusting the dose, consider the patient's clinical condition; Hb variability; Hb rate of rise and rate of decline; and Vafseo responsiveness. A single Hb excursion may not require a dosing change.
If the Hb level exceeds 13 g/dL, interrupt the dose of Vafseo until Hb is less than or equal to 12 g/dL then resume with dose that is 150 mg less than dose prior to interruption.
If the Hb rises rapidly (e.g., more than 1 g/dL in any 2-week period or more than 2 g/dL in 4 weeks), interrupt or adjust the dose as indicated in Table 1 below.
Treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb levels is not achieved. Alternative explanations for an inadequate response should be sought and treated before re-starting Vafseo (see Table 1).

Table 1: Vafseo dose titration

Change in Hb value	**Less than 10 g/dL**	**10 to 12 g/dL**	**Greater than 12 g/dL but less than**	**13 g/dL or greater**

			13 g/dL	
<u>No rise</u> in Hb greater than 1 g/dL in 2-week period or more than 2 g/dL in 4 weeks	150 mg increase if no dose increase in past 4 weeks	Maintain dose	150 mg reduction	Interrupt the dose of Vafseo until Hb is less than or equal to 12 g/dL then resume with dose that is 150 mg less than dose prior to interruption. If patient was on 150 mg prior to interruption, then resume with 150 mg.
Hb rise more than 1 g/dL in any 2-week period or more than 2 g/dL in 4 weeks	150 mg reduction or maintain* dose	150 mg reduction or maintain* dose	150 mg reduction	

* Dose reduction may not be required in case of a single Hb value.

Monitoring

When initiating or adjusting therapy, monitor Hb levels every two weeks until stable, then monitor at least monthly.

ALT, AST, and bilirubin must be evaluated prior to the initiation of Vafseo, monthly for three months after initiation and as clinically indicated thereafter (see section 4.4).

<u>Important administration instructions</u>

Evaluation of iron stores and nutritional factors
Evaluate the iron status in all patients before and during treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%.

Oral iron and phosphate binders

Vafseo should be administered at least 1 hour before oral iron supplements, products whose primary component consists of iron or iron-containing phosphate binders. As vadadustat may form a chelate with multivalent cations, Vafseo should be administered at least 1 hour before or 2 hours after non-iron-containing phosphate binders or other medicinal products whose primary component consists of multivalent cations such as calcium, magnesium or aluminium (see section 4.5).

Other causes of anaemia

Assess other causes of anaemia (e.g., vitamin deficiency, other metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating Vafseo.

Missed dose

If a dose is missed, patients should take the dose as soon as they remember during the same day and then patients should take the next dose at the usual time the next day. Patients should not take a double dose.

Special population

Elderly

No dose adjustment is recommended for elderly patients (see section 5.2).

Renal impairment

No dose adjustment is needed in patients with renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment is needed in patients with mild or moderate hepatic impairment.
Vafseo is not recommended for use in patients with severe hepatic impairment (Child-Pugh class C) as the safety and efficacy have not been evaluated in this population (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Vafseo in the paediatric population have not been established. No data are available.

Method of administration

The film-coated tablet is administered orally with or without food and should be swallowed whole without chewing.
Vafseo can be taken at any time before, during, or after dialysis.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Cardiovascular and mortality risk

In controlled clinical trials, patients with dialysis-dependent (DD) CKD treated with Vafseo, experienced similar risks for major cardiovascular events (all-cause mortality, non-fatal stroke and non-fatal myocardial infarction), compared to darbepoetin alfa (see section 5.1).

In controlled clinical trials, patients with non-dialysis-dependent (NDD) CKD treated with Vafseo experienced greater risks for major cardiovascular events (all-cause mortality, non-fatal stroke and non-fatal myocardial infarction) compared to darbepoetin alfa (see section 5.1). Since the safety of vadadustat has not been established in NDD patients with CKD, Vafseo should not be administered in patients with NDD-CKD.

Patients with signs and symptoms of serious adverse cardiovascular reactions or stroke should be promptly evaluated and treated according to standard of care. The decision to interrupt or discontinue treatment should be based on a benefit-risk consideration for the individual patient.

Thromboembolic events

Thromboembolic events such as vascular access thrombosis (VAT) (arteriovenous graft thrombosis and arteriovenous fistula thrombosis) were reported as very common amongst the patients from two active-controlled DD-CKD clinical trials (see section 4.8). Therefore, patients with pre-existing risk factors for thromboembolic events and prior history of thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident) should be monitored carefully.

VAT is a common occurrence in patients receiving hemodialysis therefore patients should be monitored carefully.

Patients with signs and symptoms of thromboembolic events should be promptly evaluated and treated according to standard of care. The decision to interrupt or discontinue treatment should be based on a benefit-risk consideration for the individual patient.

Hepatic impairment

Vafseo is not recommended for use in patients with severe hepatic impairment (Child-Pugh class C) (see sections 4.2 and 5.2).

Hepatotoxicity

An increase in ALT, AST (frequency common) and/or bilirubin (frequency uncommon) attributed to Vafseo was reported (see section 4.8). ALT, AST, and

bilirubin must be evaluated prior to the initiation of Vafseo, monthly for three months after initiation and as clinically indicated thereafter (see section 4.2).

Vafseo must be discontinued if ALT or AST elevations > 3x Upper Limit of Normal (ULN) are accompanied by a bilirubin increase > 2x ULN, or if there is persistent ALT or AST > 3x ULN (see sections 4.2 and 4.8).

Worsening of hypertension

Hypertension is one of the leading causes of CKD and is also a complication of CKD. Administration of Vafseo in patients with CKD may be associated with worsening of hypertension (see section 4.8). Blood pressure should be monitored before initiation and regularly thereafter at a frequency determined by a patient's individual situation and local clinical practices. Patients should be advised on the importance to comply with antihypertensive therapy and monitoring of blood pressure.

Seizures

Seizures were commonly reported in patients receiving vadadustat (see section 4.8). Vadadustat should be used with caution in patients with a history of seizures or fits, epilepsy or medical conditions associated with a predisposition to seizure activity such as central nervous system (CNS) infections. The decision to interrupt or discontinue treatment should be based on a benefit-risk consideration for the individual patient.

Initial decrease in Hb levels in patients converting from ESA

Hb levels may initially decrease when converting patients from an ESA to Vafseo especially in patients who were on high baseline ESA doses. Generally, the higher the baseline ESA dose, the deeper the initial decrease in Hb levels will be before levels gradually return to baseline Hb by Weeks 16 to 20 (see section 5.1 for course of Hb during treatment in individual studies). Rescue therapy such as RBC transfusion or ESA treatment may be considered during the transition phase if a Hb values fall below 9.0 g/dL or if response is considered not acceptable. Patients receiving RBC transfusions are recommended to continue Vafseo treatment during the transfusion period. Vafseo should be paused temporarily during ESA rescue treatment and may be resumed when Hb levels are ≥10 g/dL (see section 4.2).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per dosage, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Vadadustat was an inducer of CYP2B6 in *in vitro* experiments. However, this interaction has not been examined *in vivo*.

Effect of other medicinal products on the pharmacokinetics of vadadustat

Iron supplements, phosphate binders and other medicinal products whose primary component consists of multivalent cations.

Co-administration with oral iron supplements (e.g., ferric citrate, ferrous sulphate, sodium ferrous citrate), products whose primary component consists of iron, iron-containing phosphate binders (e.g., ferric citrate, sucroferric oxyhydroxide) and non-iron-containing phosphate binders (calcium acetate, sevelamer carbonate) decreases the exposure (C_{max} and AUC) of vadadustat. The co-administration of each oral iron-based drug reduced the bioavailability of vadadustat up to 90% and 92% in terms of the AUC_{∞} and C_{max}. The co-administration of non-iron-containing phosphate binders reduced the bioavailability of vadadustat up to 55% and 52% for AUC_{∞} and C_{max}.

Vafseo should be administered at least 1 hour before oral iron supplements, products whose primary component consists of iron or iron-containing phosphate binders. As vadadustat may form a chelate with multivalent cations, Vafseo should be administered at least 1 hour before or 2 hours after non-iron-containing phosphate binders or other medicinal products whose primary component consists of multivalent cations such as calcium, magnesium or aluminium.

Organic anion transporter (OAT) OAT1/OAT3 inhibitors

Co-administration with probenecid, an OAT1/OAT3 inhibitor, increased vadadustat AUC values almost 2-fold. If co-administration with strong or moderate OAT1 or OAT3 inhibitors (e.g. benzylpenicillin, teriflunomide, or p-aminohippuric acid) occurs, patients should be managed cautiously and evaluated for excessive effects of vadadustat. For potential adverse reactions and dose adjustment in case of rapid Hb rise please refer to sections 4.8 and 4.2.

Effect of vadadustat on the pharmacokinetics of other medicinal products

BCRP substrates

Vadadustat may increase the AUC of BCRP substrates when co-administered. Dose adjustment of co-prescribed BCRP substrates may be needed. The following have been studied (see Table 2).

Table 2: Potential clinically significant drug interactions between vadadustat and BCRP substrates

Co-administered medicinal product	Effect on concentration	Clinical comment
Sulfasalazine	4.5-fold ↑ sulfasalazine AUC;	Monitor for signs of adverse effects

	no substantial change in active metabolites exposure	of sulfasalazine.
Simvastatin	~2-fold ↑ simvastatin AUC	Consider limiting the dose of simvastatin in CKD patients on Vafseo to 20 mg daily. Monitor for signs of adverse effects of simvastatin.
Rosuvastatin	2- to 3-fold ↑rosuvastatin AUC and C_{max}	Consider limiting the dose of rosuvastatin in CKD patients on Vafseo to 10 mg daily. Monitor for signs of adverse effects of rosuvastatin.

In addition to sulfasalazine, simvastatin, and rosuvastatin, monitor for signs of excessive effects of co-administered BCRP substrates such as fluvastatin, nelfinavir, pitavastatin, and topotecan, and for the need of their dose reduction.

OAT3 substrates

Vadadustat may increase the AUC of OAT3 substrates when co-administered. The AUC of furosemide (40 mg) increased 2-fold following multiple doses of Vafseo (600 mg once daily). Monitor for signs of excessive effects of co-administered OAT3 substrates such as famotidine, furosemide, methotrexate, olmesartan, sitagliptin, and zidovudine.

Dose adjustment of concomitantly administered OAT3 substrate may be needed.

CYP2B6 substrates

Vadadustat was an inducer of CYP2B6 in *in vitro* experiments. However, this interaction has not been examined *in vivo*. Co-administration of vadadustat with substrates of CYP2B6 (e.g. efavirenz, bupropion) may alter the pharmacokinetics of these drugs and therefore caution should be exercised when vadadustat is co-administered with CYP2B6 substrates.

CYP2C9 substrates

Co-administration of vadadustat (600 mg) with celecoxib (200 mg) increased celecoxib C_{max} and AUC 60% and 11%, respectively. Patients receiving warfarin or other narrow therapeutic CYP2C9 substrates (e.g., phenytoin) must therefore be managed cautiously and evaluated for excessive effects when treated with vadadustat.

CYP3A4 substrates

Based on *in vitro* data, vadadustat may have a potential for CYP3A4 downregulation. Co-administration of vadadustat with CYP3A4 substrates may alter their pharmacokinetics and therefore caution should be exercised when vadadustat is co-administered with CYP3A4 substrates.

CYP2C8 substrates

Based on *in vitro* data, vadadustat may inhibit CYP2C8 and therefore may increase exposure to CYP2C8 substrates and therefore caution should be exercised when vadadustat is co-administered with CYP2C8 substrates.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are limited data for the use of vadadustat in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, vadadustat should only be used during pregnancy if the benefit justifies the potential risk to the fetus.

Breast-feeding

It is unknown whether vadadustat is excreted in human breast milk. Available pharmacokinetic data in animals have shown excretion of vadadustat in milk (see section 5.3). A risk to the breastfed infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Vafseo therapy, taking into account the benefit of breast-feeding for the child and benefit of therapy for the woman.

Fertility

Studies in animals showed no effects of vadadustat on fertility (see section 5.3). The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

Vafseo has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions are based on pooled data from four active-controlled studies in CKD (DD and NDD patients) of 3686 patients treated with vadadustat and 3687 treated with darbepoetin alfa, including 2923 exposed for at least 6 months and 2011 exposed for greater than one year to vadadustat.

The population for vadadustat was 19 to 104 years of age, 51.2% male, and the percentage of Caucasian, Hispanic, Black (including African Americans) and Asian patients was 66%, 35.6%, 20.3%, and 5.4%, respectively.

The most frequent adverse reactions in DD-CKD and NDD-CKD patients treated with vadadustat respectively were hypertension (11.1% / 16.0%), diarrhoea (12.7% / 13.0%) and thromboembolic events (13.7% / 6.9%).

Tabulated list of adverse reactions

All adverse drug reactions (ADRs) are listed by system organ class (SOC) and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

	Very common	**Common**	**Uncommon**
Nervous systems disorders		Headache Seizures[a]	
Vascular disorders	Hypertension Thromboembolic events[a]	Hypotension Hypersensitivity	
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders	Diarrhoea	Constipation Nausea Vomiting	
Investigations		Elevated liver enzymes[b]	Blood bilirubin increased

[a]For further details please refer to "Thromboembolic events" and "Seizures" below.
[b]Includes preferred terms transaminases increased, ALT increased, AST increased, hepatic enzyme increased, liver function test abnormal

Description of selected adverse reactions

Thromboembolic events

Cerebrovascular accident events occurred in 0.8% vs 0.9% (0.5 vs 0.5 events/100 PY) of the DD-CKD population; and in 0.9% vs 0.9% (0.5 vs 0.5 events/100 patient years [PY]) of the NDD-CKD population; in the vadadustat and the darbepoetin alfa groups respectively.

Deep vein thrombosis (DVT) events occurred in 0.7% vs 0.5% (0.4 vs 0.3 events/100 PY) of the DD-CKD population; and 0.6% vs 0.6% (0.4 vs 0.3 events/100 PY) of the NDD-CKD population; in the vadadustat and darbepoetin alfa groups respectively.

Pulmonary embolism events occurred in 0.3% vs 0.5% (0.2 vs 0.3 events/100 PY) of the DD-CKD population; and in 0.3% vs 0.2% (0.2 vs 0.1 events/100 PY) of the NDD-CKD population; in the vadadustat and darbepoetin alfa groups respectively.

Transient ischaemic attack events occurred in 0.8% vs 0.4% (0.5 vs 0.3 events/100 PY) of the DD-CKD population; and in 0.7% vs 0.3% (0.4 vs 0.2 events/100 PY) of the NDD-CKD population; in the vadadustat and darbepoetin alfa groups respectively.

Acute myocardial infarction events occurred in 4.3% vs 4.2% (3.1 vs 2.9 events/100 PY) of the DD-CKD population; and in 3.8% vs 2.9% (2.2 vs 1.8 events/100 PY) of the NDD-CKD population, in the vadadustat and darbepoetin alfa groups respectively.

Arteriovenous graft thrombosis events occurred in 1.1% vs 1.1% (0.9 vs 1.0 events/100 PY) of the DD-CKD population in the vadadustat and darbepoetin alfa groups respectively.

Arteriovenous fistula thrombosis events occurred in 3.0% vs 2.3% (2.1 vs 1.6 events/100 PY) of the DD-CKD population in the vadadustat and darbepoetin alfa groups respectively.

For information on cardiovascular and mortality risk and thromboembolism please see sections 4.4 and 5.1.

Elevated liver enzymes and blood bilirubin increased

Hepatocellular injury attributed to vadadustat was uncommonly reported for the pooled population (in less than 0.2% of DD-CKD and NDD-CKD patients). The majority of the events were non-serious, and all events were asymptomatic and resolved after discontinuation of vadadustat. The time to onset was generally within the first 3 months of treatment. Abnormal liver enzymes tests: elevated serum ALT (3x ULN), AST (3x ULN), and bilirubin (2x ULN) were seen in 1.8%, 1.8% and 0.3% of patients treated with vadadustat, respectively.

There was one serious adverse event of hepatocellular injury with jaundice in an NDD-CKD clinical trial patient which occurred approximately 8 weeks after initiating vadadustat. This case was multifactorial and resolved after vadadustat and other concomitant medicinal products were discontinued. This single case did not meet Hy's law criteria due to a significantly elevated alkaline phosphatase (ALP), which preceded the bilirubin elevation, indicating cholestasis as a contributing factor to the elevated bilirubin.

Seizures

In DD-CKD patients, seizures occurred in 1.6% (1.1 patients with events per 100 PY of exposure) in the vadadustat group, and 1.6% (1.3 patients with events per 100 PY of exposure) in the darbepoetin alfa group (see section 4.4).

In NDD-CKD patients, seizures occurred in 0.7% (0.4 patients with events per 100 PY of exposure) in the vadadustat group, and 0.8% (0.5 patients with events per 100 PY of exposure) in the darbepoetin alfa group (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Vadadustat overdose may result in extensions of the pharmacologic effects such as increased Hb and secondary polycythemia. Symptoms of vadadustat overdose should be managed as clinically appropriate (e.g., reduction of Vafseo dose or discontinuation) and careful monitoring and treated as clinically indicated. Approximately 16% of the vadadustat dose is removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-anaemic preparations, other anti-anaemic preparations, ATC code: B03XA08

Mechanism of action

Vadadustat is a hypoxia-inducible factor prolyl-hydroxylase inhibitor which leads to increased cellular levels of hypoxia-inducible factor thereby stimulating endogenous erythropoietin (EPO) production, increasing iron mobilization and RBC production, resulting in a gradual rate of rise in Hb (see Figures 1, 2, 3 and 4).

Pharmacodynamic effects

After a single dose of vadadustat (80 mg to 1200 mg) in healthy male subjects, a dose-dependent increase in EPO was observed.

Cardiac electrophysiology

Vadadustat did not cause any clinically significant QTc prolongation following a 600 mg and 1200 mg dose.

Clinical efficacy and safety

The efficacy and safety of vadadustat given once daily for the treatment of anaemia in adult patients with CKD was demonstrated compared to darbepoetin alfa in global multi-centre, randomised, active-controlled, non-inferiority, open-label studies of 3923 DD patients. and 3476 NDD patients.

Patients with diagnosis of NDD-CKD with an eGFR > 60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation at screening were excluded from pivotal studies.

Patients were randomised 1:1 to receive vadadustat with a starting dose of 300 mg once daily or darbepoetin alfa administered subcutaneously or intravenously as per prescribing information for 52 weeks to assess the efficacy endpoints. Vadadustat was titrated in increments of 150 mg up to 600 mg to achieve the patient's Hb target. After 52 weeks, patients were continued study treatment to assess long-term safety until the event-driven major adverse cardiovascular event (MACE) endpoints were reached. The primary efficacy endpoint for each study was the difference in mean change of Hb from baseline to the primary evaluation period (Weeks 24 to 36). The key secondary efficacy endpoint was the difference in mean change of Hb from baseline to the secondary evaluation period (Weeks 40 to 52). The primary safety endpoint was time to first MACE. MACE was defined as all-cause mortality, non-fatal myocardial infarction and non-fatal stroke.

Treatment of anaemia in dialysis-dependent patients

Two studies ($INNO_2VATE$ 1 and $INNO_2VATE$ 2) were conducted in adult DD-CKD patients with baseline Hb values between 8.0 to 11.0 g/dL in the United States (US) and 9.0 to 12.0 g/dL outside the US. $INNO_2VATE$ 1 included patients with incident DD-CKD who initiated dialysis within 16 weeks of beginning their trial participation and who were ESA-naive, had limited prior ESA use or were maintained on ESAs. $INNO_2VATE$ 2 included patients on chronic maintenance dialysis for more than 12 weeks who had converted from prior ESA therapy. In both studies, vadadustat was non-inferior to darbepoetin alfa in correcting and maintaining or maintaining Hb levels across geographic-specific target Hb ranges [10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL in Europe and rest of world (ROW)] at weeks 24 to 36 and weeks 40 to 52 in adult DD-CKD patients with anaemia. Results for the primary and secondary efficacy endpoints are provided in Table 3. Course of Hb during treatment in individual studies is provided in Figure 1 and Figure 2. Examination of age, gender, race and region subgroups did not identify differences in response to vadadustat among these subgroups.

Table 3 **INNO$_2$VATE STUDIES**

	INNO$_2$VATE 1		INNO$_2$VATE 2	
Hb (g/dL)	**Vadadustat N = 181**	**Darbepoetin alfa N = 188**	**Vadadustat N = 1777**	**Darbepoet alfa N = 1777**
Baseline mean (SD)	9.37 (1.07)	9.19 (1.14)	10.25 (0.85)	10.23 (0.83
Primary endpoint Weeks 24 to 36 mean (SD)	10.36 (1.13)	10.61 (0.94)	10.36 (1.01)	10.53 (0.96
Adjusted mean change from baseline (LSM) [95% CI]	1.26 [1.05, 1.48]	1.58 [1.37, 1.79]	0.19 [0.12, 0.25]	0.36 [0.29 0.42]
Estimated treatment difference [95% CI] vadadustat – darbepoetin alfa	-0.31 [-0.53, -0.10]		-0.17 [-0.23, -0.10]	
Key secondary endpoint Weeks 40 to 52 mean (SD)	10.51 (1.19)	10.55 (1.14)	10.40 (1.04)	10.58 (0.98
Adjusted mean change from baseline (LSM) [95% CI]	1.42 [1.17, 1.68]	1.50 [1.23, 1.76]	0.23 [0.16, 0.29]	0.41 [0.34 0.48]
Estimated treatment difference [95% CI] vad adustat – darbepoetin alfa	-0.07 [-0.34, 0.19]		-0.18 [-0.25, -0.12]	

CI: confidence interval; LSM: least squares mean; SD: standard deviation

Figure 1: Mean (+/-SD) of change from baseline in Hb (g/dL) for INNO$_2$VATE 1 incident dialysis

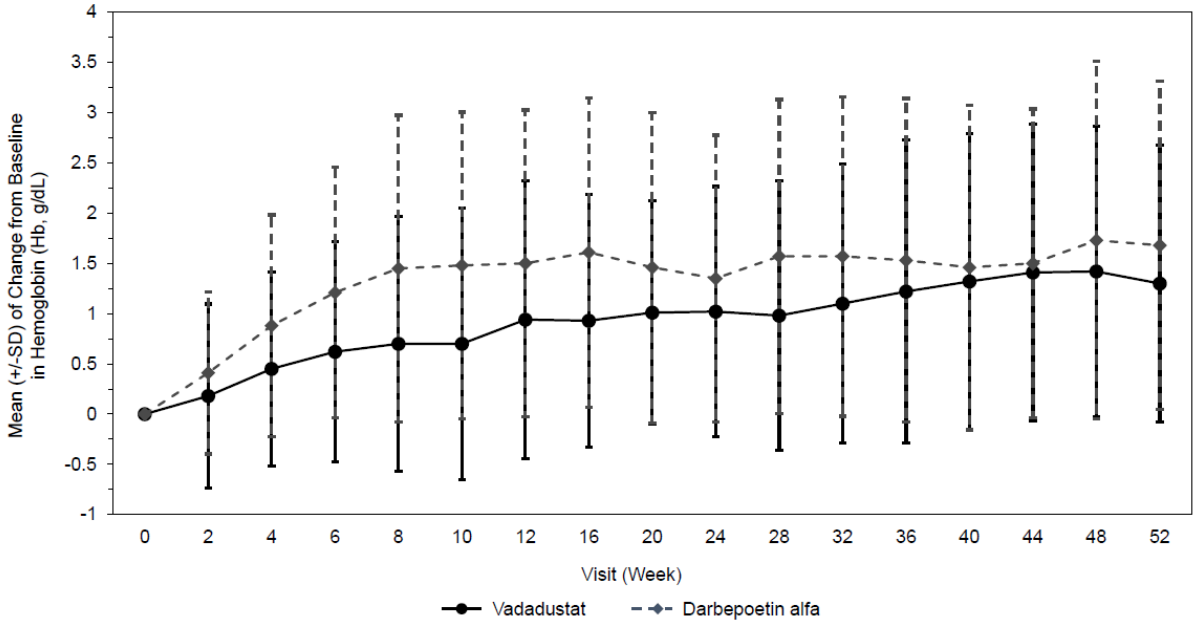
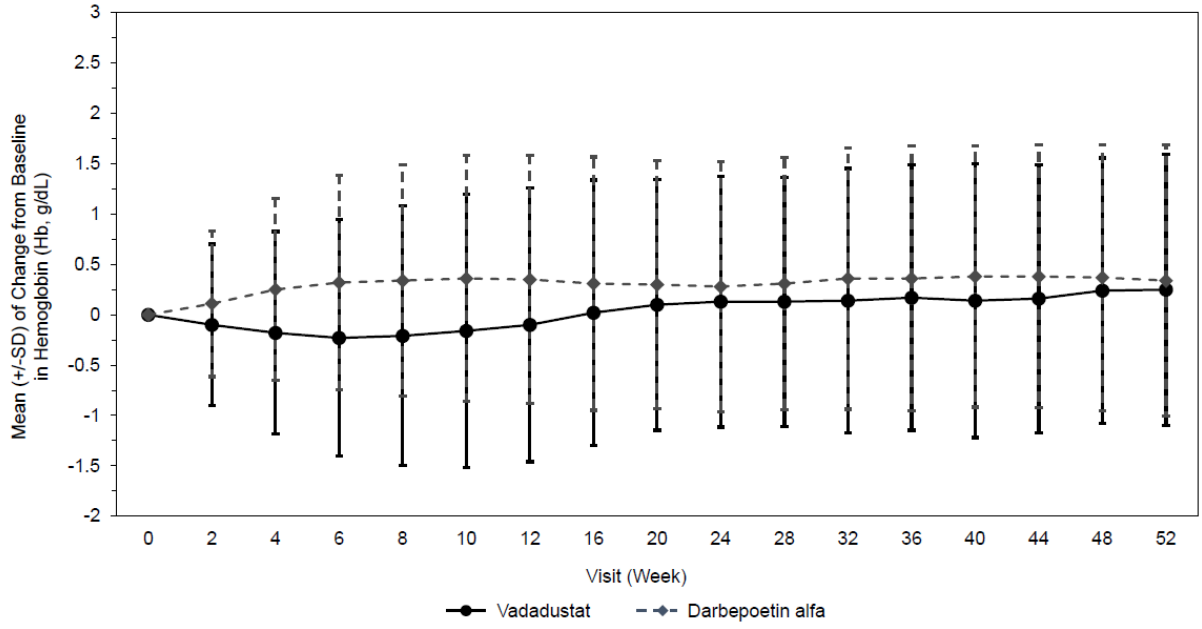


Figure 2: Mean (+/-SD) of change from baseline in Hb (g/dL) for INNO$_2$VATE 2 prevalen dialysis



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Cardiovascular outcomes - dialysis-dependent CKD patients

The incidence of MACE was evaluated as part of the long-term safety evaluation of the two global efficacy studies in DD-CKD patients. Vadadustat met the composite primary safety endpoint defined as non-inferiority of vadadustat to darbepoetin alfa in time to occurrence of MACE for the global study population (1.3 NI margin [HR (95% CI) was 0.96 (0.83, 1.11)]. The results were consistent for the primary endpoint and the individual components of the primary endpoint (see Table 4). The results for the primary MACE endpoint were also supported by the results from key secondary endpoints using expanded MACE definitions. These results showed that vadadustat did not decrease the time to MACE plus hospitalization for heart failure; MACE

plus thromboembolic events excluding vascular access; cardiovascular (CV) MACE (all-cause mortality, non-fatal MI or non-fatal stroke); CV death or all-cause mortality compared to darbepoetin.

Table 4: INNO$_2$VATE analysis* of the composite 3-point MACE and individual cardiovascular endpoints

	Vadadustat N = 1947 n (%)	**Darbepoetin alfa N = 1955 n (%)**	**Hazard ratio [95% CI]**
Any major adverse cardiovascular events (MACE)	355 (18.2)	377 (19.3)	0.96 [0.83, 1.11]
All-cause mortality	253 (13.0)	253 (12.9)	
Non-fatal myocardial infarction	76 (3.9)	87 (4.5)	
Non-fatal stroke	26 (1.3)	37 (1.9)	

*The MACE analyses were conducted on randomised subjects who received at least 1 dose of study treatment.
CI: confidence interval; MACE: major adverse cardiovascular events.

Treatment of anaemia in non-dialysis-dependent patients

Two studies (PRO$_2$TECT 1 and PRO$_2$TECT 2) were conducted in NDD-CKD adult patients. PRO$_2$TECT 1 included patients diagnosed with CKD with baseline Hb values less than 10.0 g/dL and who were not previously treated with an ESA. PRO$_2$TECT 2 included patients diagnosed with CKD with baseline Hb levels between 8.0 and 11.0 g/dL in the US and between 9.0 and 12.0 g/dL outside of the US who were previously treated with an ESA for anaemia. In both studies, vadadustat was non-inferior to darbepoetin alfa in correcting and maintaining or maintaining Hb levels across geographic-specific target Hb ranges [10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL in Europe and ROW] at weeks 24 to 36 and weeks 40 to 52 in adult NDD-CKD patients with anaemia (see Figures 3 and 4). Results for the primary and secondary efficacy endpoints are provided in Table 5. Examination of age, gender, race and region subgroups did not identify differences in response to vadadustat among these subgroups.

Table 5: PRO$_2$TECT STUDIES

	PRO$_2$TECT 1		**PRO$_2$TECT 2**	
Hb (g/dL)	**Vadadustat N = 879**	**Darbepoetin alfa N = 872**	**Vadadustat N = 862**	**Darbepoetin alfa N = 863**
Baseline mean (SD)	9.11 (0.80)	9.14 (0.78)	10.42 (0.89)	10.39 (0.94)
Primary	10.39 (0.99)	10.35 (1.03)	10.77 (0.98)	10.77 (0.99)

endpoint Weeks 24 to 36 mean (SD)				
Adjusted mean change from baseline (LSM) [95 % CI]	1.43 [1.34, 1.52]	1.38 [1.29, 1.47]	0.41 [0.34, 0.48]	0.42 [0.35, 0.49]
Estimated treatment difference [95% CI] vadadustat – darbepoetin alfa	0.05 [-0.04, 0.15]		-0.01 [-0.09, 0.07]	
Key secondary endpoint Weeks 40 to 52 mean (SD)	10.48 (1.05)	10.45 (1.01)	10.8 (1.04)	10.79 (1.05)
Adjusted mean change from baseline (LSM) [95% CI]	1.52 [1.42, 1.62]	1.48 [1.38, 1.59]	0.43 [0.35, 0.52]	0.44 [0.35, 0.52]
Estimated treatment difference [95% CI] vadadustat – darbepoetin alfa	0.04 [-0.06, 0.14]		-0.00 [-0.10, 0.09]	

CI: confidence interval; LSM: least squares mean; SD: standard deviation

Figure 3: Mean (+/-SD) of change from baseline in Hb (g/dL) for PRO$_2$TECT 1 ESA naive

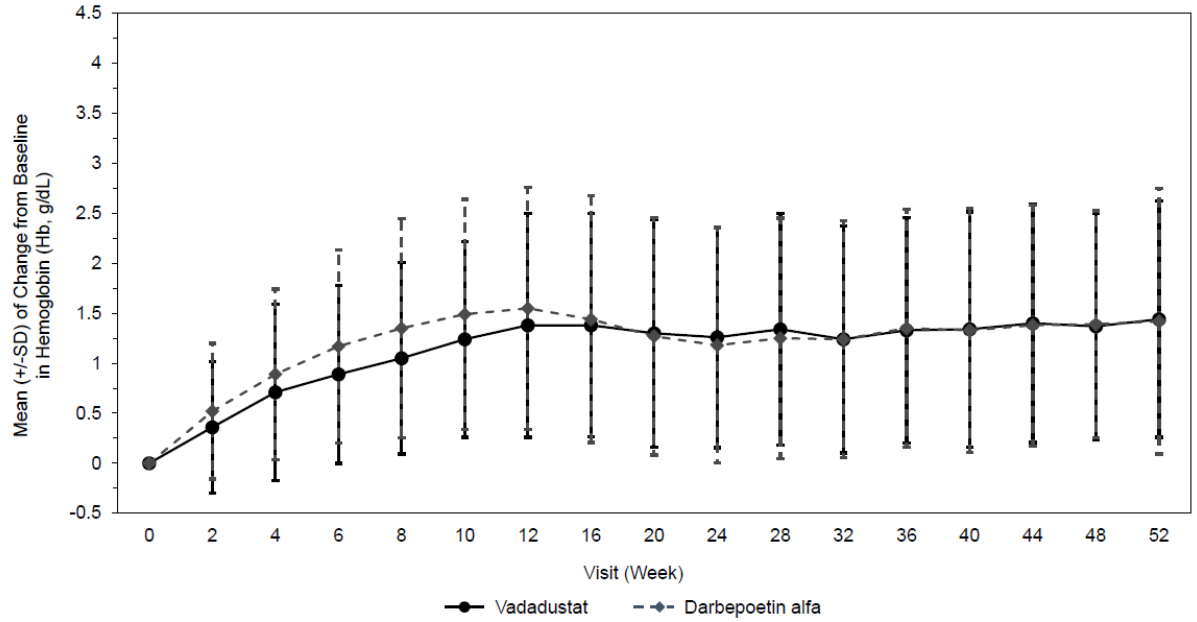
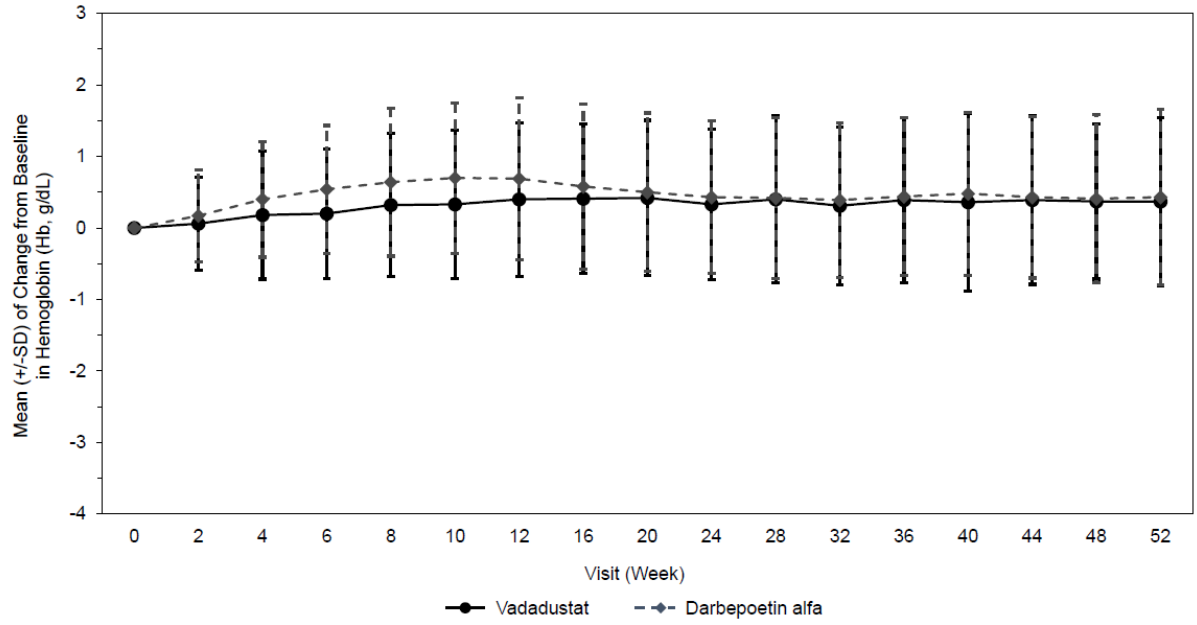


Figure 4: Mean (+/-SD) of change from baseline in Hb (g/dL) for PRO$_2$TECT 2 ESA treated



Cardiovascular outcomes - non-dialysis-dependent CKD patients

The incidence of MACE was assessed as part of the long-term safety evaluation of the two global efficacy studies in NDD-CKD patients. Vadadustat did not meet the composite primary safety endpoint defined as non-inferiority of vadadustat to darbepoetin alfa in time to first occurrence of MACE (all-cause mortality, non-fatal MI or non-fatal stroke) for the global study population. The HR (95% CI) was 1.17 (1.012, 1.36*) with the upper bound exceeding the pre-specified non-inferiority margin of 1.3 (see Table 6). The difference between the two treatments with respect to MACE (38 patients

or 2.1%) was driven primarily by non-fatal myocardial infarction (22 patients (1.3%)) and all-cause mortality (10 patients (0.5%)).

Table 6: PRO_2TECT analysis* of the composite 3-point MACE and individual cardiovascular endpoints

	Vadadustat N = 1739 n (%)	**Darbepoetin alfa N = 1732 n (%)**	**Hazard ratio [95% CI]**
Any major adverse cardiovascular events (MACE)	382 (22.0)	344 (19.9)	1.17 [1.01, 1.36]
All-cause mortality	284 (16.3)	274 (15.8)	
Non-fatal myocardial infarction	66 (3.8)	44 (2.5)	
Non-fatal stroke	32 (1.8)	26 (1.5)	

*The MACE analyses were conducted on randomised subjects who received at least 1 dose of study treatment.
CI: confidence interval; MACE: major adverse cardiovascular events

Paediatric population

The Agency has deferred the obligation to submit the results of studies with Vafseo in one or more subsets of the paediatric population for the treatment of symptomatic anaemia associated with CKD on chronic maintenance dialysis as per paediatric investigation plan (PIP) decision, for the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Vadadustat is rapidly absorbed after single and repeated oral doses. Median time to peak plasma concentrations (T_{max}) is approximately 2 to 3 hours. No significant accumulation has been observed after repeated dosing.

Distribution

Vadadustat is highly protein bound (greater than or equal to 99.5% in human plasma). Vadadustat does not distribute into RBC.

Biotransformation

Vadadustat is primarily metabolised via glucuronidation by UDP-glucuronosyltransferase (UGT) enzymes to O-glucuronide conjugates.

Elimination

When compared to healthy subjects, patients with NDD-CKD demonstrated an increase in mean half-life from 4.8 to 7.9 hours. The half-life for patients on chronic haemodialysis was only modestly longer at 9.2 hours. After a single oral dose of radiolabelled vadadustat 650 mg to healthy adults, 85.9% of the dose was recovered (58.9% in urine and 26.9% in faeces). The excretion for vadadustat (unchanged form) was less than 1% in urine and about 9% in faeces.

Linearity/non-linearity

The pharmacokinetics (AUC and C_{max}) of vadadustat are linear and increase proportional to dose after single doses from 80 mg to 1200 mg.

Pharmacokinetic/pharmacodynamic relationship(s)

Pharmacokinetics in special populations

Renal impairment

Vadadustat clearance decreased with decreasing estimated glomerular filtration rate (eGFR) in NDD-CKD patients and exposures in dialysis patients were approximately 2-fold higher compared to healthy subjects. In patients with DD-CKD, no significant differences in pharmacokinetics (C_{max}, AUC or mean half-life) were observed when vadadustat was administered 4 hours before dialysis or 2 hours after dialysis.

Hepatic impairment

Data from 8 patients with moderate hepatic impairment (Child-Pugh Class B) showed a small increase in AUC (6%) which is not expected to have clinical significance. The half-life and apparent total body clearance for vadadustat were comparable between subjects with normal hepatic function and subjects with moderate hepatic function. However, caution in this patient group is recommended. Vadadustat has not been studied in severe hepatic impairment (Child-Pugh Class C).

Age, gender, race, and body weight

Population pharmacokinetic analysis did not suggest any clinically significant effects of age (19 to 104 years), gender, race, or body weight (47 to 118 kg) on the pharmacokinetics of vadadustat.

A sensitivity analysis at body weight extremes (30.1 to 204 kg) showed that the dose titration algorithm resulted in predicted Hb levels at the limits of the predefined window of 10 to 12 g/dL. Therefore, no dose-adjustment is proposed at body weight extremes.

5.3 Preclinical safety data

In nonclinical studies, mortalities were observed in mice, rats, rabbits and dogs due to exaggerated pharmacological effects such as polycythemia and hyperviscosity of the blood, leading to thrombosis and organ infarct at dose levels that were clinically relevant (starting from exposure multiples of 0.04 to the maximum recommended therapeutic dose of 600 mg).

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicology, genotoxicity or carcinogenic potential.

Vadadustat was not teratogenic in either the rat or the rabbit up to the highest dose level tested (160 mg/kg/day and 50 mg/kg/day, respectively), corresponding to 1.7 and 0.16 times the human exposure at the 600 mg dose, respectively, in the dams. Development effects were noted only in the rat at dose levels corresponding to 1.7 times the human exposure at the 600 mg dose; characterised as a decrease in fetal body weight and an increased incidence of a reduction in skeletal ossification, both of which were considered secondary to the decline in body weight and food consumption in the pregnant dams. However, in a rat dose finding study, at doses that caused significant maternal toxicity, there was an increase in postimplantation loss at $\geq$ 120 mg/kg/day and decreased fetal body weight at 240 mg/kg/day, but no teratogenicity.

Vadadustat was excreted in the milk in rats with a ratio of milk to plasma of up to 14.49.

Fertility and early embryonic development and prenatal and postnatal development reproduction toxicity studies were conducted in female and male rats at dose levels of 40 to 120 mg/kg/day. Vadadustat did not impact rat fertility or reproduction.

Whilst animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity the potential risk for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Sodium starch glycolate
Hypromellose
Colloidal silicon dioxide
Magnesium stearate

Tablet coating

Polyvinyl alcohol
Macrogol/Polyethylene glycol (PEG)
Talc

Vafseo150 mg film-coated tablets
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium foil blisters

Pack size: 28 Tablets

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

MEDICE Arzneimittel Pütter GmbH & Co. KG
Kuhloweg 37
58638 Iserlohn
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 11243/0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 May 2023

10 DATE OF REVISION OF THE TEXT

04/06/2024