**ANNEX I**

**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
Vafseo 300 mg film-coated tablets
Vafseo 450 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vafseo 150 mg film-coated tablets

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

Vafseo 300 mg film-coated tablets

Each 300 mg film-coated tablet contains 300 mg of vadadustat

Vafseo 450 mg film-coated tablets

Each 450 mg film-coated tablet contains 450 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 8 mm in diameter, debossed with “VDT” on one side and “150” on the other side.

Vafseo 300 mg film-coated tablets

Oval, yellow tablets 8 mm in width, 13 mm in length, debossed with “VDT” on one side and “300” on the other side.

Vafseo 450 mg film-coated tablets

Oval, pink tablets 9 mm in width, 15 mm in length debossed with “VDT” on one side and “450” 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

Vadadustat should be initiated by a physician experienced in the management of anaemia. All other causes of anaemia should be evaluated prior to initiating therapy with Vafseo, and when deciding to increase the dose.

Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. In addition to the presence of symptoms of anaemia, criteria such as rate of fall of haemoglobin (Hb) concentration, prior response to iron therapy, and the risk of needing of red blood cell (RBC) transfusion could be considered in the evaluation of the individual patient's clinical course and condition.

Posology

*Evaluation before administration*

*Evaluation of iron stores and nutritional factors*

Iron status should be evaluated in all patients before and during treatment. Supplemental iron therapy should be administered when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%.

*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 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. Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently.

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 | 13 g/dL or greater |
|---|---|---|---|---|
| **No rise 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).

*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 populations

*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 has 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.

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).

## 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 death, myocardial infarction and stroke compared to darbepoetin alfa (see section 5.1).

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 were reported as very common amongst the patients from two active-controlled clinical trials in CKD (see section 4.8). Therefore, patients with pre-existing risk factors for thromboembolic event and prior history of thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident) 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 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

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 practice. Patients should be advised on the importance to comply with antihypertensive therapy and monitoring of blood pressure.

Convulsions

Convulsions were commonly reported in patients receiving vadadustat (see section 4.8). Vadadustat should be used with caution in patients with a history of convulsions or fits, epilepsy or medical conditions associated with a predisposition to convulsion 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 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).

Inadequate response to therapy

Inadequate response to therapy with vadadustat should prompt a search for causative factors. A reticulocyte count should be considered as part of the evaluation. If typical causes of non-response are excluded, and the patient has reticulocytopenia, an examination of the bone marrow should be considered. In the absence of an addressable cause for an inadequate response by 24 weeks of therapy, Vafseo should be discontinued.

Misuse

Misuse may lead to an excessive increase in red blood cell volume. This may be associated with life-threatening complications.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

Vadadustat was metabolically stable *in vitro* and metabolism via cytochrome P450s (CYPs) was minimal. The metabolic pathways involved were oxidation and mainly glucuronidation. The major circulating metabolite vadadustat-O-glucuronide was catalyzed by multiple uridine 5`-diphospho-glucuronosyltransferases (UGTs, UGT1A1, 1A7, 1A8 and 1A9).

Vadadustat has potentially clinically relevant interactions with breast cancer resistance protein (BCRP) substrates, OAT3 substrates, OAT1/3 inhibitors and CYP2C9 substrates with a narrow therapeutic index.

Vadadustat induced CYP2B6, inhibited CYP2C8 and caused down-regulation of CYP3A4 in *in vitro* experiments. However, these interactions have 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 which contain 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 oral iron-based medicinal products reduced the bioavailability of vadadustat up to 90% and 92% in terms of the $AUC_{\infty}$ and $C_{max}$.

The co-administration of non-iron-containing phosphate binders reduced the bioavailability of vadadustat up to 55% and 52% for $AUC_{\infty}$ 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 and some statins*

Vadadustat may increase the AUC of BCRP substrates, and some statins 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, and select statins**

| **Co-administered medicinal product** | **Effect on concentration** | **Clinical comment** |
|---|---|---|
| sulfasalazine | 4.5-fold ↑ sulfasalazine AUC; no substantial change in active metabolites exposure | Monitor for signs of adverse events of sulfasalazine. |
| simvastatin | ~2-fold ↑ simvastatin AUC | Limit the top dose of simvastatin in patients with CKD on Vafseo to 20 mg daily. Monitor for signs of adverse events of simvastatin. |
| rosuvastatin | 2- to 3-fold ↑rosuvastatin AUC and $C_{max}$ | Limit the top dose of rosuvastatin in patients with CKD on Vafseo to 10 mg daily. Monitor for signs of adverse events 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 the co-administered OAT3 substrates such as famotidine, furosemide, methotrexate, olmesartan, sitagliptin, and zidovudine.

Dose adjustment of concomitantly administered OAT3 substrate may be needed.

*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.

*CYP2B6 substrates*

Vadadustat is an *in vitro* inducer of CYP2B6. Co-administration of vadadustat with sensitive substrates of CYP2B6 (e.g. efavirenz, bupropion) may alter their pharmacokinetics, and therefore caution should be exercised when vadadustat is co-administered with CYP2B6 substrates.

*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, it is preferable to avoid the use of vadadustat during pregnancy.

Breast-feeding

It is unknown whether vadadustat is excreted in human milk. Available pharmacokinetic data in animals have shown excretion of vadadustat in milk (for details, see section 5.3). A risk to infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue vadadustat 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 two active-controlled studies in DD-CKD of 1947 patients treated with Vafseo and 1955 treated with darbepoetin alfa, including 1514 exposed for at least 6 months and 1047 exposed for greater than one year to Vafseo.

The most frequent (> 10%) adverse reactions in patients treated with vadadustat are thromboembolic events (13.7%), diarrhoea (12.7%) and hypertension (11.1%).

The most frequent (≥ 1%) serious adverse reactions in patients treated with vadadustat are thromboembolic events (10.0%), hypotension (1.6%) and hypertension (1.1%).

Tabulated list of adverse reactions

All adverse 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) and are show in Table 3.

**Table 3: Adverse reactions**

| | **Very common** | **Common** | **Uncommon** |
|---|---|---|---|
| **Nervous systems disorders** | | Headache<br>Convulsions[a] | |
| **Vascular disorders** | Hypertension<br>Thromboembolic events[a] | Hypotension<br>Hypersensitivity | |
| **Respiratory, thoracic and mediastinal disorders** | | Cough | |
| **Gastrointestinal disorders** | Diarrhoea | Constipation<br>Nausea<br>Vomiting<br>Abdominal pain upper | |
| **Investigations** | | Elevated liver enzymes[b] | Blood bilirubin increased |

a) for further details, please refer to "Thromboembolic events" and "Convulsions"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) in the vadadustat and darbepoetin alfa groups respectively.

Deep vein thrombosis (DVT) events occurred in 0.7% vs 0.5% (0.4 vs 0.3 events/100 PY) 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) 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) 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) 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) 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) 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 Vafseo was uncommonly reported (in less than 0.2% of patients). The majority of events were non-serious, asymptomatic and resolved after discontinuation of Vafseo. 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%, 1.4% and 0.3% of patients treated with Vafseo, 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 Vafseo. This case was multifactorial and resolved after Vafseo 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.

*Convulsions*

In DD-CKD patients, convulsions occurred in 1.6% (1.1 patients with events per 100 patient years of exposure) in the vadadustat group, and 1.6% (1.3 patients with events per 100 patient years 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 national reporting system listed in Appendix V.

## 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 (eg, 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 red blood cell production, resulting in gradual rate of rise in Hb (see Figures 1 and 2).

Cardiac electrophysiology

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

Clinical efficacy and safety

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

The population in DD-CKD for Vafseo was 19 to 93 years of age, 55.9% male, and the percentage of Caucasian, Hispanic, Black (including African Americans) and Asian patients was 64.5%, 38.5%, 24.1%, and 4.5%, respectively.

In both studies, non-inferiority of vadadustat to darbepoetin alfa was to be concluded if the lower bound of the 95% CI for the difference in estimated mean change in average Hb from Baseline in the 2 treatment groups was greater than the prespecified non-inferiority margin of -0.75 g/dL. Patients were randomised 1:1 to receive Vafseo 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. Vafseo was titrated in increments/reductions 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 (MI) and non-fatal stroke.

*Treatment of anaemia*

The two studies INNO$_2$VATE 1 and INNO$_2$VATE 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$_2$VATE 1 included patients with incident DD-CKD who initiated dialysis within 16 weeks of beginning their trial participation and who were erythropoiesis-stimulating agent (ESA)-naïve, had limited prior ESA use or were maintained on ESAs. INNO$_2$VATE 2 included patients on chronic maintenance dialysis for more than 12 weeks who had converted from prior ESA therapy. In both studies, Vafseo met the primary Hb endpoint according to predefined noninferiority margin (- 0.75 g/dL). Results for the primary and secondary efficacy endpoints are provided in Table 4. Course of Hb during treatment in individual studies is provided in Figure 1 and Figure 2.

**Table 4: INNO$_2$VATE studies**

| | **INNO$_2$VATE 1** | | **INNO$_2$VATE 2** | |
|---|---|---|---|---|
| **Hb (g/dL)** | **Vafseo N = 181** | **Darbepoetin Alfa N = 188** | **Vafseo N = 1777** | **Darbepoetin 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] |
| **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] |
| 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 correction**

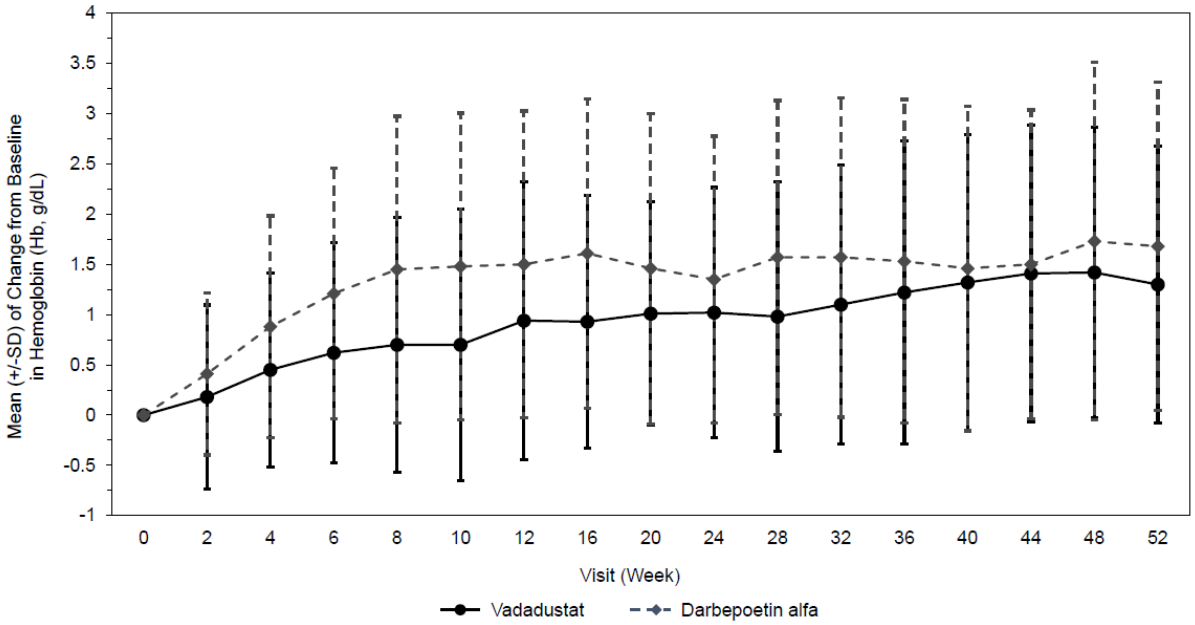
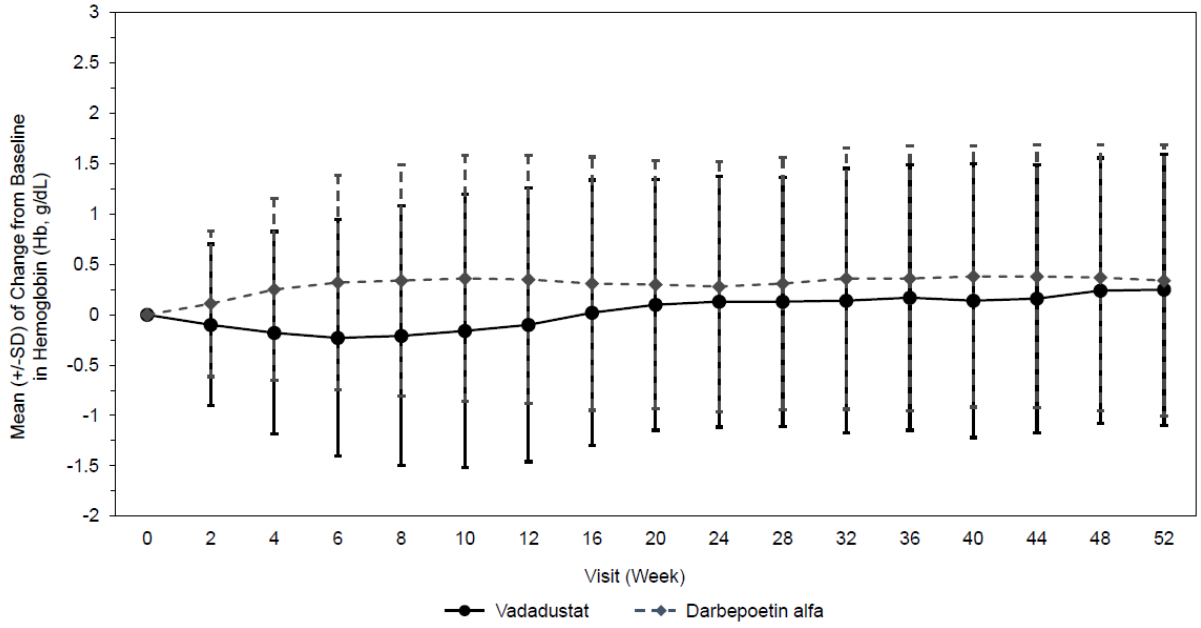



**Figure 2: Mean (+/-SD) of change from baseline in Hb (g/dL) for INNO$_2$VATE 2 conversion**




*Cardiovascular outcomes*

The incidence of major adverse cardiovascular events (MACE) was evaluated as part of the long-term safety evaluation of the two global efficacy studies in DD-CKD patients. Vafseo met the composite primary safety endpoint defined as non-inferiority of Vafseo 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)]) (see Table 5).

**Table 5: INNO$_2$VATE analysis* of the composite 3-point MACE and individual cardiovascular endpoints**

| | Vafseo 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.

Paediatric population

The European Medicines 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 anaemia associated with chronic disorders (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 in healthy subjects.

Vafseo may be administered with or without food. Administration of a 450 mg Vafseo tablet with a standard high-fat meal decreased $C_{max}$ by 27% and decreased the AUC by 6%, relative to fasted conditions.

Distribution

Vadadustat is highly protein bound (greater than or equal to 99.5% in human plasma). The mean blood to plasma ratio was less than 1 (0.50 to 0.55) suggesting minimal sequestration into red blood cells (RBCs). In patients with CKD the apparent volume of distribution (Vd/F) was 11.6 L.

Biotransformation

Vadadustat is primarily metabolised via direct glucuronidation by UDP-glucuronosyltransferase (UGT) enzymes to O-glucuronide conjugates. The major metabolite vadadustat-O-glucuronide (15% of the AUC of plasma radioactivity). Vadadustat acyl glucuronide (0.047% of the total radioactivity in plasma) is a minor metabolite. Vadadustat metabolites are not active.

Elimination

The half-life of vadadustat in DD-CKD patients was 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.

Pharmacokinetics in special populations

*Renal impairment*

Vadadustat exposures in DD-CKD patients were approximately 2-fold higher compared to healthy subjects. No significant differences in pharmacokinetics ($C_{max}$, AUC or mean half-life) were observed when Vafseo was administered 4 hours before dialysis or 2 hours after dialysis.

*Hepatic impairment*

Moderate hepatic impairment (Child-Pugh Class B) did not significantly affect the AUC or $C_{max}$ of vadadustat compared to healthy subjects. The half-life and apparent total body clearance for vadadustat were comparable between subjects with normal hepatic function and subjects with moderate hepatic function. 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 non-clinical trials, 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 reveal no other special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, 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 (based on AUC in NDD-CKD patients), 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 foetal 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 ≥ 120 mg/kg/day and decreased foetal 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core

Microcrystalline cellulose (E 460)
Sodium starch glycolate
Hypromellose (E 464)
Silica, colloidal anhydrous (E 551)
Magnesium stearate

Tablet coating

Polyvinyl alcohol (E 1203)
Macrogol (E 1521)
Talc (E 553b)
Titanium dioxide (E 171)
Yellow iron oxide (E 172) (Vafseo 300 mg film-coated tablets)
Iron oxide red (E 172) (Vafseo 450 mg film-coated tablets)
Ferrosoferric oxide (E 172) (Vafseo 450 mg film-coated tablets)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Vafseo 150 mg film-coated tablets

28 tablets in 2 PVC/aluminium foil blisters with 14 x 150 mg film-coated tablets
98 tablets in 7 PVC/aluminium foil blisters with 14 x 150 mg film-coated tablets

Vafseo 300 mg film-coated tablets

28 tablets in 2 PVC/aluminium foil blisters with 14 x 300 mg film-coated tablets
98 tablets in 7 PVC/aluminium foil blisters with 14 x 300 mg film-coated tablets

Vafseo 450 mg film-coated tablets

28 tablets in 2 PVC/aluminium foil blisters with 14 x 450 mg film-coated tablets
98 tablets in 7 PVC/aluminium foil blisters with 14 x 450 mg film-coated tablets

Not all pack sizes may be marketed.

### 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

AKEBIA EUROPE Limited
70 Sir John Rogerson’s Quay
Dublin 2
Co. Dublin
D02 R296
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1725/001
EU/1/23/1725/002
EU/1/23/1725/003
EU/1/23/1725/004
EU/1/23/1725/005
EU/1/23/1725/006

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Millmount Healthcare Limited
Block-7, City North Business Campus,
Stamullen, Co. Meath,
K32 YD60
Ireland

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Vafseo 150 mg film-coated tablets
vadadustat

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg vadadustat

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
98 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AKEBIA EUROPE Limited
70 Sir John Rogerson's Quay
Dublin 2
Co. Dublin
D02 R296
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1725/001
EU/1/23/1725/002
EU/1/23/1725/003
EU/1/23/1725/004
EU/1/23/1725/005
EU/1/23/1725/006

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Vafseo 150 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vafseo 150 mg film-coated tablets
vadadustat

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Akebia

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Vafseo 300 mg film-coated tablets
vadadustat

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg vadadustat

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
98 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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EU/1/23/1725/004
EU/1/23/1725/005
EU/1/23/1725/006

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Vafseo 300 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vafseo 300 mg film-coated tablets
vadadustat

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

AKEBIA

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Vafseo 450 mg film-coated tablets
vadadustat

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 450 mg vadadustat

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
98 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AKEBIA EUROPE Limited
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## 12. MARKETING AUTHORISATION NUMBER(S)

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EU/1/23/1725/002
EU/1/23/1725/003
EU/1/23/1725/004
EU/1/23/1725/005
EU/1/23/1725/006

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Vafseo 450 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Vafseo 450 mg film-coated tablets
vadadustat

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

AKEBIA

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Vafseo 150 mg film-coated tablets**
**Vafseo 300 mg film-coated tablets**
**Vafseo 450 mg film-coated tablets**
vadadustat

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


1. What Vafseo is and what it is used for
2. What you need to know before you take Vafseo
3. How to take Vafseo
4. Possible side effects
5. How to store Vafseo
6. Contents of the pack and other information


## 1. What Vafseo is and what it is used for

Vafseo is a medicine that increases the amount of haemoglobin (the protein in your red blood cells that carries oxygen around the body) and the number of red blood cells in your blood. It contains the active substance vadadustat.

Vafseo is used to treat symptomatic anaemia (low levels of red blood cells or haemoglobin in your blood) that is associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis. When the amount of haemoglobin or the number of red blood cells is low, the cells in your body might not receive enough oxygen. Anaemia can cause symptoms such as tiredness, weakness, or shortness of breath.

**How Vafseo works**
Vafseo increases the level of a substance called “Hypoxia-Inducible Factor” (HIF), which increases the production of red blood cells when oxygen levels are low. By raising HIF levels, Vafseo increases the production of red blood cells and raises the levels of haemoglobin. This improves the oxygen supply to your body and may reduce your anaemia symptoms.

## 2. What you need to know before you take Vafseo

**Do not take Vafseo**
- if you are allergic to vadadustat or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Vafseo if you:

- had **blood clots** in the past and/or have risk factors for blood clots. This medicine increases the production of red blood cells and this may increase the risk of developing blood clots. Examples of risk factors are:
  - being overweight
  - diabetes
  - heart diseases
  - being off your feet for a long time because of surgery or illness
  - taking oral contraceptives

  It is important that you tell your doctor about previous heart attack, stroke, blood clots or risk factors so your doctor can decide if this medicine is a suitable treatment for your anaemia. Talk to your doctor immediately if you think you have developed a blood clot. You can find a description of possible blood clot symptoms below in section 4.
- have **high blood pressure** (hypertension). Vafseo may worsen your high blood pressure. Therefore, it is very important that you take your high blood pressure medicines regularly and that you frequently check your blood pressure.
- have **severe liver disease.**
- have a **convulsion** or fit or possible warning signs that a convulsion may occur, such as headache, irritability, fear, confusion or unusual feelings
- are converting from **high doses of erythropoiesis-stimulating agent (ESA)** because you might require red blood cell transfusion or supplemental ESA while the doctor is adjusting your Vafseo dose.

Talk to your doctor or pharmacist before taking Vafseo if you have any of the conditions mentioned above.

Misuse can lead to an increase in red blood cells and consequently thicken the blood. This can cause life-threatening problems with the heart or blood vessels.

*Blood tests*
Chronic kidney disease can cause anaemia, which may increase the risk of heart and blood vessel problems and even death. Therefore, it is important to treat your anaemia. Your doctor will regularly check the amount of haemoglobin in your blood.
The treatment may increase liver enzymes. Your doctor will regularly check the amount of these enzymes in your blood at the start of your treatment and then monthly for the first 3 months of your treatment.

**Children and adolescents**
Do not give Vafseo to children and adolescents aged under 18 years. There is not enough information about its use in this age group.

**Other medicines and Vafseo**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Vafseo may affect the way other medicines work, and medicines may affect how Vafseo works.

In particular, tell your doctor or pharmacist if you have taken, or are taking any of the following medicines:
- Medicines to reduce phosphate levels in your blood (called **phosphate binders**) such as **sevelamer carbonate** or **calcium acetate** and medicines or supplements that **contain iron** such as **ferric citrate**, **sucroferric oxyhydroxide**, **ferrous sulphate**, **sodium ferrous citrate**.
- **probenecid**, a medicine used to treat gout
- **sulfasalazine**, a medicine to treat severe bowel and rheumatic joint inflammation
- medicines known as **statins** to reduce cholesterol levels in your blood (examples include **simvastatin, rosuvastatin, fluvastatin** or **pitavastatin**)
- **furosemide** or **olmesartan**, medicines used to treat high blood pressure
- **nelfinavir, efavirenz** or **zidovudine**, medicines used to treat HIV
- **topotecan**, a medicine used to treat cancer

- **famotidine**, a medicine to treat stomach ulcers
- **methotrexate**, a medicine used to treat cancer and autoimmune disorders
- **sitagliptin**, a medicine to treat diabetes
- **celecoxib**, a medicine to treat pain and inflammation
- **warfarin**, a medicine used to stop blood clotting
- **phenytoin**, a medicine used to treat epilepsy
- **benzylpenicillin**, a medicine used to treat infections
- **teriflunomide**, a medicine used to treat multiple sclerosis
- **p-aminohippuric acid**, a diagnostic substance used in tests involving the kidney
- **bupropion**, a medicine used to treat depression

Your doctor will decide how you should use these medicines during your treatment with Vafseo.

**Pregnancy, breast-feeding and fertility**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
It is not known whether vadadustat passes into human milk.
Your doctor will decide whether you can take Vafseo during pregnancy or breast-feeding.
It is not known if Vafseo has an effect on your fertility.

**Driving and using machines**
Vafseo is unlikely to affect your ability to drive and use machines.

**Vafseo contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

## 3. How to take Vafseo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**Your dose**
Your doctor will tell you what dose of Vafseo to take. Treatment with Vafseo will usually start at a daily dose of 300 mg. Thereafter, your doctor may either increase or decrease your daily dose in steps of 150 mg. The lowest dose is 150 mg per day and the highest dose is 600 mg per day.
Always take Vafseo as prescribed by your doctor.

It is important that your doctor regularly checks the amount of haemoglobin in your blood. Based on these test results your doctor may increase or lower your dose. If the amount of haemoglobin in your blood becomes too high your treatment will be stopped. Do not restart your treatment until your doctor tells you to do so and use only the dose your doctor prescribes.

**Taking Vafseo**
- Vafseo film-coated tablets are taken by mouth with water.
- Take your Vafseo tablet whole and without chewing or crushing the tablet.
- Take your Vafseo dose once every day.
- Vafseo can be taken with food or between meals.
- You can take Vafseo at any time before, during, or after dialysis

*Phosphate binders and Vafseo*
If you are treated with phosphate binders which do not include iron (such as sevelamer carbonate or calcium acetate) or medicines containing calcium, magnesium or aluminium you should take Vafseo at least 1 hour before or 2 hours after taking those medicines, because otherwise vadadustat will not be

properly absorbed by your body. If the phosphate binder you are taking contains iron, see the information below.

*Iron containing products and Vafseo*
If you take medicines containing iron or phosphate binders containing iron you should take Vafseo at least 1 hour before those products. Vadadustat will not be properly absorbed by your body if you do not follow these instructions.

**If you take more Vafseo than you should**
If you take more tablets or a higher dose than you should, contact your doctor straight away.

**If you forget to take Vafseo**
- Do not take a double dose to make up for a forgotten dose. Do not take two tablets on one day.
- If **more than 24 hours** (1 day) remains before your next scheduled dose: take the missed dose as soon as possible and take the next dose on the next scheduled day.
- If **less than 24 hours** (1 day) remains before your next scheduled dose: skip the missed dose and take the next dose on the next scheduled day.

**If you stop taking Vafseo**
If you stop taking Vafseo, your anaemia may get worse. Do not stop taking this medicine unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Possible serious side effects**
Contact your doctor **straight away** if you get any of the following:

**Very common** (may affect more than 1 in 10 people)
- high blood pressure (hypertension)
- blood clots (thromboembolic events) which may lead to:
  - heart attack (myocardial infarction), with symptoms such as pain in chest and/or other parts of the body, feeling dizzy, shortness of breath, feeling or being sick, sense of anxiety
  - stroke (cerebrovascular accident), with symptoms such as sudden severe headache, seizures (fits), loss of coordination, loss of balance
  - blood clot in a blood vessel in the lungs (pulmonary embolism), with symptoms such as pain in your chest or upper back, difficulty breathing, coughing up blood
  - blood clot in a vein, such as in the leg (known as deep vein thrombosis), with symptoms such as painful swelling and redness
  - “mini stroke” (TIA), with symptoms such as speech and visual disturbance, and numbness or weakness in the face, arms and legs
  - stenosis (arteriovenous fistula thrombosis and arteriovenous graft thrombosis), with symptoms such as purplish, bulging veins seen through the skin, similar to varicose veins.

**Other possible side effects**
Talk to your doctor if you get any of the following side effects:

**Very common** (may affect more than 1 in 10 people)
- diarrhoea

**Common** (may affect up to 1 in 10 people)

- headache
- convulsions
- low blood pressure (hypotension)
- hypersensitivity
- cough
- constipation
- feeling sick
- vomiting
- upper stomach pain
- increased liver enzymes

**Uncommon** (may affect up to 1 in 100 people)
- increased amount of bilirubin (a breakdown product of red blood cells) in your blood

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Vafseo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Vafseo contains**

Vafseo 150 mg film-coated tablets
- The active substance is vadadustat. Each film-coated tablet contains 150 mg vadadustat.

Vafseo 300 mg film-coated tablets
- The active substance is vadadustat. Each film-coated tablet contains 300 mg vadadustat.

Vafseo 450 mg film-coated tablets
- The active substance is vadadustat. Each film-coated tablet contains 450 mg vadadustat

The other ingredients are:

Tablet core

Microcrystalline cellulose (E 460), sodium starch glycolate, hypromellose (E 464), silica, colloidal anhydrous (E 551), magnesium stearate. See section 2 “Vafseo contains sodium”.

Tablet coating

Polyvinyl alcohol (E 1203), macrogol (E 1521), talc (E 553b), titanium dioxide (E 171), yellow iron oxide (E 172) (only for 300 mg), iron oxide red (E 172) and ferrosoferric oxide (E 172) (both only for 450 mg).

**What Vafseo looks like and contents of the pack**
Vafseo 150 mg film-coated tablets are round and white, debossed with "VDT" on one side and "150" on the other side.
Vafseo 300 mg film-coated tablets are oval and yellow, debossed with "VDT" on one side and "300" on the other side.
Vafseo 450 mg film-coated tablets are oval and pink, debossed with "VDT" on one side and "450" on the other side.

Vafseo film-coated tablets are supplied in cartons containing 28 or 98 film-coated tablets in PVC/aluminium foil blisters.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
AKEBIA EUROPE Limited
70 Sir John Rogerson's Quay
Dublin 2
Co. Dublin
D02 R296
Ireland

**Manufacturer**
Millmount Healthcare Limited
Block-7, City North Business Campus
Stamullen, Co. Meath, K32 YD60
Ireland

For any information about this medicine, please contact the Marketing Authorisation Holder.

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.