

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **AUSTRALIAN PRODUCT INFORMATION – Vafseo® (VADADUSTAT) TABLETS**

### **1 NAME OF THE MEDICINE**

Vadadustat

### **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 List of excipients.

### **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.

#### Vafseo 300 mg film-coated tablets

Oval, yellow tablets debossed with “VDT” on one side and “300” on the other side.

#### Vafseo 450 mg film-coated tablets

Oval, pink tablets 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 anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

### Dosage

#### 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. The ESA must be stopped before initiating Vafseo.

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 Pharmacodynamic properties 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 cells (RBC) transfusion or ESA treatment may be considered during the transition phase if Hb values fall below 90 g/L or response is considered not acceptable (see section 4.4 Special warnings and precautions for use). 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  $\geq 100$  g/L. 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 100 to 120 g/L.

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 130 g/L, interrupt the dose of Vafseo until Hb is less than or equal to 120 g/L then resume with dose that is 150 mg less than dose prior to interruption.
- If the Hb rises rapidly (e.g., more than 10 g/L in any 2-week period or more than 20 g/L 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 Table1).

**Table 1: Vafseo dose titration**

Change in Hb value	Current Hb value			
	Less than 100 g/L	100 to 120 g/L	Greater than 120 g/L but less than 130 g/L	130 g/L or greater
<b>No rise in Hb greater than 10 g/L in 2-week period or more than 20 g/L in 4 weeks</b>	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 120 g/L 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.
<b>Hb rise more than 10 g/L in any 2-week period or more than 20 g/L in 4 weeks</b>	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 Special warnings and precautions for use.

### **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.

### **Dosage adjustment**

#### Elderly

No dose adjustment is recommended for elderly patients, see section 5.2 Pharmacokinetic properties.

### Renal impairment

No dose adjustment is needed in patients with renal impairment, see section 5.2

Pharmacokinetic properties.

### 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 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

## **Important administration instructions**

### 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, phosphate binders and other medicinal products whose primary component consists of multivalent cations

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 Interactions with other medicines and other forms of interactions).

### 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.

### 4.3 CONTRAINDICATIONS

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

### 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 myocardial infarction [MI]), compared to darbepoetin alfa (see section 5.1 Pharmacodynamic properties).

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 clinical trials in CKD (see section 4.8 Adverse effects (undesirable effects)). 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 haemodialysis, 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 section 5.2 Pharmacokinetic properties). Limited data is available in patients with moderate hepatic impairment (see section 5.2 Pharmacokinetic Properties).

#### **Hepatotoxicity**

An increase in ALT, AST and/or bilirubin attributed to Vafseo was reported (see section 4.8 Adverse effects (undesirable effects)). 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 Dose and method of administration).

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 Dose and method of administration, and 4.8 Adverse effects (undesirable effects)).

### **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 Adverse effects (undesirable effects)). 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**

Vafseo 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. Seizures were reported in patients receiving vadadustat (see section 4.8 Adverse effects (undesirable effects)). 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 Pharmacodynamic properties 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 90 g/L 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  $\geq 100$  g/L (see section 4.2 Dose and Method Administration).

### **Use in the elderly**

No dose adjustment is recommended for elderly patients, see section 5.2 Pharmacokinetic properties.

### Paediatric use

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

### Effects on laboratory tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

### 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), oral products which 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  $AUC_{\infty}$  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 Adverse effects (undesirable effects) and 4.2 Dose and Method Administration.

## 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 drug	Effect on concentration	Clinical comment
Sulfasalazine	4.5-fold ↑ sulfasalazine AUC; no substantial change in active metabolites exposure	Monitor for signs of adverse effects 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 <sub>max</sub>	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 considered to be 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**

### **Effects on fertility**

Vadadustat did affect male or female fertility in rats at oral doses up to 120 mg/kg/day (yielding exposure [AUC] only marginally above that of patients at the maximum recommended human dose). The potential risk for humans is unknown.

### **Use in pregnancy – Pregnancy Category C**

There are limited data for the use of vadadustat in pregnant women.

Vadadustat did not cause malformations or embryofetal lethality 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 exposure in patients at the maximum recommended human dose of 600 mg. Development effects were noted only in the rat at 160 mg/kg/day, yielding 1.7 times the human exposure at the 600 mg dose; characterised as a decrease in foetal body weight and a reduction in skeletal ossification, both of which were considered secondary to the decline in body weight and food consumption in the pregnant dams.

These embryofetal development studies offer only limited support for safety due to exposure in animals being below or only slightly higher than in patients. Vadadustat and/or its metabolites were shown to cross the placenta in rats, and the potential for adverse effects on development resulting from pharmacological activity in the foetus cannot be excluded. Vafseo should only be used during pregnancy if the benefit justifies the potential risk to the foetus.

## Use in lactation

It is unknown whether vadadustat is excreted in human breast milk. Vadadustat and/or its metabolites were shown to be readily excreted in milk in rats, with peak concentrations in milk more than double that in plasma, and overall exposure (AUC) more than six times greater. Vafseo should not be used in a woman who is breastfeeding given the risk of pharmacologically-mediated adverse events in the child. 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.

## 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### Summary of the safety profile

The adverse events (AE) are based on pooled data from two active-controlled studies in DD-CKD of 1947 patients treated with vadadustat and 1955 treated with darbepoetin alfa, including 1514 exposed for at least 6 months and 1047 exposed for greater than one year to vadadustat. The population for vadadustat 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.

The most frequent AEs reported in the vadadustat and darbepoetin alfa treatment groups were thromboembolic events (13.7% and 12.0%, respectively), diarrhoea (12.7% and 10.0%, respectively), hypertension (11.1% and 13.6%, respectively), and pneumonia (10.7% and 9.6%, respectively).

Death was reported for 11.9% and 13.9% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively.

Table 3 lists the adverse events that occurred in at least 5% or greater of DD-CKD patients.

**Table 3: Adverse events occurring in ≥ 5% of DD-CKD patients**

Adverse event	Patients treated with vadadustat (N = 1947)	Patients treated with darbepoetin alfa (N = 1955)
<b>Vascular disorders</b>		
Hypertension	11.1%	13.6%
Hypotension	7.9%	8.0%
<b>Gastrointestinal disorders</b>		

<b>Adverse event</b>	<b>Patients treated with vadadustat (N = 1947)</b>	<b>Patients treated with darbepoetin alfa (N = 1955)</b>
Diarrhoea	12.7%	10.0%
Nausea	8.4%	7.5%
Vomiting	6.8%	6.9%
<b>Cardiac disorders</b>		
Atrial fibrillation	3.8%	5.2%
<b>Infections and infestations</b>		
Pneumonia	10.7%	9.6%
Urinary tract infection	6.2%	6.8%
Upper respiratory tract infection	5.3%	6.2%
Nasopharyngitis	5.2%	4.7%
Sepsis	4.9%	5.6%
<b>Injury, poisoning and procedural complications</b>		
Fall	8.3%	8.6%
Arteriovenous fistula thrombosis	5.8%	4.5%
Dialysis related complication	5.4%	6.8%
Arteriovenous fistula site complication	5.2%	6.6%
<b>Metabolism and nutrition disorders</b>		
Fluid overload	8.7%	9.2%
Hyperkalaemia	8.6%	10.3%
<b>Musculoskeletal and connective tissue disorders</b>		
Pain in extremity	5.1%	6.3%
Back pain	4.3%	5.3%
<b>Nervous systems disorders</b>		
Headache	8.6%	7.5%
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	5.6%	6.4%
Dyspnoea	5.4%	6.6%

#### Description of selected serious adverse events

##### *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 MI events occurred in 4.3% vs 4.2% (3.1 vs 2.9 events/100 P.Y) 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 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic properties.

#### Description of adverse events (less than 5%)

##### *Elevated liver enzymes and blood bilirubin increased*

Hepatocellular injury attributed to vadadustat was uncommonly reported for the DD-CKD population (in less than 0.2% of patients). The majority of 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%, 1.4% and 0.3% of DD-CKD 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 Special warnings and precautions for use).

#### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 OVERDOSE

Vadadustat overdose may result in extensions of the pharmacologic effects such as increased Hb and secondary polycythaemia. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

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

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of action

Vadadustat is an inhibitor of hypoxia-inducible factor prolyl-hydroxylase (HIF-PH), a group of enzymes that degrade a subunit of hypoxia-inducible factor (HIF) in the presence of oxygen under normal physiological conditions. HIF mediates tissue adaptation to low oxygen environments through transcriptional regulation of gene expression. Decreased HIF-PH activity with vadadustat leads to increased cellular levels of HIF thereby stimulating endogenous erythropoietin (EPO) production, increasing iron mobilization and red blood cell production, resulting in a gradual rate of rise in Hb.

#### 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 trials

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 two global multi-centre, randomised, active-controlled, non-inferiority, open-label studies in DD patients (3923 adult DD-CKD patients were included in these studies with 1947 patients treated with vadadustat).

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 MI and non-fatal stroke.

### Treatment of anaemia

The two studies INNO<sub>2</sub>VATE 1 and INNO<sub>2</sub>VATE 2 were conducted in adult DD-CKD patients with baseline Hb values between 80.0 to 110.0 g/L in the United States (US) and 90.0 to 120.0 g/L outside the US. INNO<sub>2</sub>VATE 1 included patients with incident DD-CKD who initiated dialysis within 16 weeks of beginning their trial participation and who were ESA-naïve, had limited prior ESA use or were maintained on ESAs. INNO<sub>2</sub>VATE 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 [100.0 to 110.0 g/L in the US and 100.0 to 120.0 g/L 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 4. 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 4: INNO<sub>2</sub>VATE STUDIES**

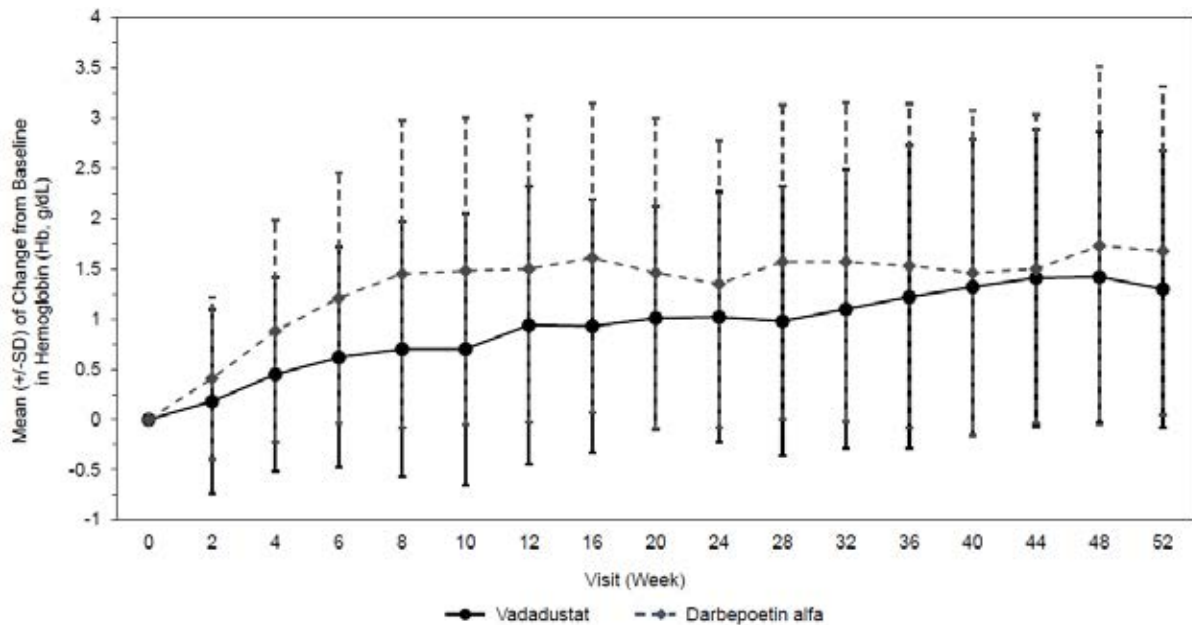
	INNO <sub>2</sub> VATE 1		INNO <sub>2</sub> VATE 2	
Hb (g/L)	Vadadustat N = 181	Darbepoetin alfa N = 188	Vadadustat N = 1777	Darbepoetin alfa N = 1777
<b>Baseline mean (SD)</b>	93.7 (10.7)	91.9 (11.4)	102.5 (8.5)	102.3 (8.2)
<b>Primary endpoint Weeks 24 to 36 mean (SD)</b>	103.6 (11.3)	106.1 (9.4)	103.6 (10.1)	105.3 (9.6)
<b>Adjusted mean change from baseline (LSM) [95% CI]</b>	12.6 [10.5, 14.8]	15.8 [13.7, 17.9]	1.9 [1.2, 2.5]	3.6 [2.9, 4.2]

AusPAR - Vafseo - vadadustat - Adjutor Healthcare Pty Ltd - PM-2022-00525-1-6  
 Date of finalisation: 11 December 2024. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

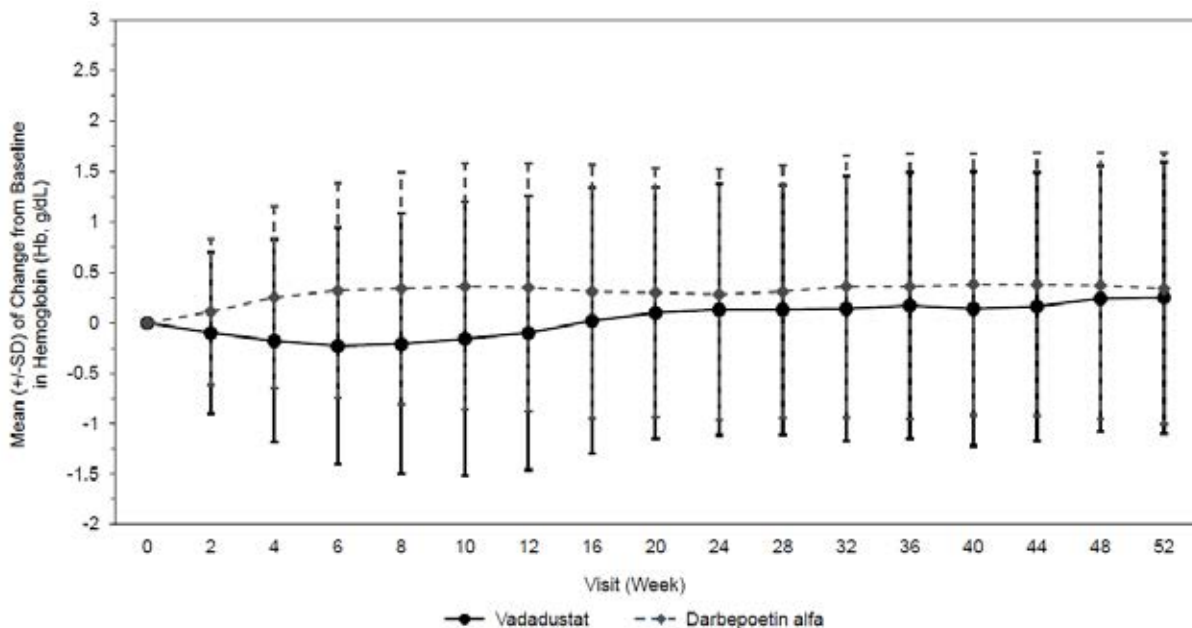
	INNO <sub>2</sub> VATE 1		INNO <sub>2</sub> VATE 2	
Hb (g/L)	Vadadustat N = 181	Darbepoetin alfa N = 188	Vadadustat N = 1777	Darbepoetin alfa N = 1777
Estimated treatment difference [95% CI] vadadustat - Darbepoetin Alfa	-3.1 [-5.3, -1.0]		-1.7 [-2.3, -1.0]	
Key secondary endpoint Weeks 40 to 52mMean (SD)	105.1 (11.9)	105.5 (11.4)	104.0 (10.4)	105.8 (9.8)
Adjusted mean change from baseline (LSM) [95% CI]	14.2 [11.7, 16.8]	15.0 [12.3, 17.6]	2.3 [1.6, 2.9]	4.1 [3.4, 4.8]
Estimated treatment difference [95% CI] vadadustat - darbepoetin alfa	-0.7 [-3.4, 1.9]		-1.8 [-2.5, -1.2]	

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

**Figure 1: Mean (+/-SD) of change from baseline in Hb (g/dL) for INNO<sub>2</sub>VATE 1 incident dialysis**



**Figure 2: Mean (+/-SD) of change from baseline in Hb (g/dL) for INNO<sub>2</sub>VATE 2 prevalent dialysis**



Cardiovascular outcomes

The incidence of MACE was evaluated as part of the long-term safety evaluation of the two global efficacy studies in DD-CKD patients. The composite primary safety endpoint was time to occurrence of MACE for the global study population. The HR for vadadustat compared with



darbepoetin was 0.96 (95% CI: 0.83, 1.11) was within the pre-specified non-inferiority margin of 1.3 for the upper bound of the 95% CI. The results were consistent for the primary endpoint and the individual components of the primary endpoint (see Table 5). 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 5: INNO<sub>2</sub>VATE analysis\* of the composite 3-point MACE and individual cardiovascular endpoints**

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

## 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 red blood cells.

### Metabolism

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

## Excretion

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.

## 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.

## 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 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 93 years), gender, race, or body weight (32 to 204 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 100 to 120 g/L. Therefore, no dose-adjustment is proposed at body weight extremes.

### 5.3 PRECLINICAL SAFETY DATA

#### Genotoxicity

Vadadustat was negative for mutagenicity in bacteria (Ames test), while positive results for clastogenicity were returned in the *in vitro* chromosomal aberration assay (in Chinese Hamster Ovary cells in the absence of metabolic activation). Positive results for genotoxicity were also obtained in an *in vitro* assay for DNA damage (GreenScreen assay in two human cell lines; examining induction of reporter gene expression), but only at cytotoxic concentrations. *In vivo*, vadadustat was not clastogenic in peripheral blood lymphocytes isolated from rats dosed orally at 60 mg/kg/day for 5 days, nor did it cause DNA damage in liver cells (Comet assay) in rats given a single oral dose up to 2000 mg/kg. Based on the weight of evidence, vadadustat is not considered genotoxic.

#### Carcinogenicity

The carcinogenic potential of vadadustat was evaluated in a 6-month study in transgenic (Tg.rasH2) mice and in a 2-year study in rats, both conducted by the oral route. Vadadustat was not carcinogenic in either species up to the highest dose levels tested (50 mg/kg/day in mice and 20 mg/kg/day in rats). Plasma exposure at the highest doses tested in animals was 3.6 - 4.8 times lower than that in humans at the maximum recommended human dose (MRHD) of 600 mg/day, and this limits the predictive value of the studies.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Each film-coated tablet of Vafseo contains the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, hypromellose, silicon dioxide and magnesium stearate.

#### *Film-coating*

Vafseo 150 mg film-coated tablets: Opadry® II White 85F18422

Vafseo 300 mg film-coated tablets: Opadry® II Yellow 85F12374

Vafseo 450 mg film-coated tablets: Opadry® II Pink 85F94586

### 6.2 INCOMPATIBILITIES

Not applicable.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

### 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.

#### Vafseo 300 mg film-coated tablets

28 tablets in 2 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.

Not all pack sizes may be marketed.

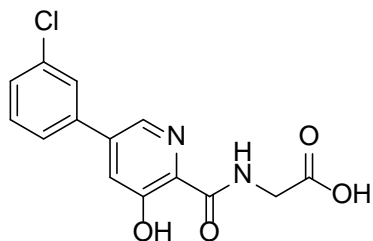
### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### Chemical structure

Vadadustat is white to off-white solid with molecular formula of  $C_{14}H_{11}ClN_2O_4$  and a molecular weight of 306.70. Its international union of pure and applied chemistry (IUPAC) chemical name is 2-[[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino]acetic acid and has the following structural formula:



#### CAS number

1000025-07-9

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – PRESCRIPTION ONLY MEDICINE

## 8 SPONSOR

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Vafseo® is a registered trademark of Akebia Therapeutics, Inc.

## 9 DATE OF FIRST APPROVAL

04 October 2023

## 10 DATE OF REVISION

N/A

### SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	N/A