swissmedic

Date: 11 September 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vafseo

International non-proprietary name: vadadustat
Pharmaceutical form: film-coated tablet
Dosage strength(s): 150 mg, 300 mg, 450 mg
Route(s) of administration: oral
Marketing authorisation holder: Voisin Consulting CH Sàrl
Marketing authorisation no.: 68862
Decision and decision date: approved on 19 June 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for vadadustat in the above-mentioned medicinal product.

Work-sharing procedure
The applicant requested a work-sharing procedure with the United Kingdom and Australia.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic – and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended starting dose is 300 mg once daily. The dose must not be increased more frequently than once every 4 weeks. Decreases in dose can occur more frequently.

When initiating or adjusting therapy, haemoglobin levels have to be monitored every two weeks until stable, then at least monthly. Dose adjustment should be done in increments of 150 mg within the range of 150 mg to 600 mg to achieve or maintain haemoglobin levels within 10-12 g/dL.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	17 March 2022
Formal control completed	15 April 2022
List of Questions (LoQ)	12 August 2022
Response to LoQ	11 January 2023
Preliminary decision	15 March 2023
Response to preliminary decision	30 March 2023
Labelling corrections	2 May 2023
Response to labelling corrections	21 May 2023
Final decision	19 June 2023
Decision	approval

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

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4 Nonclinical aspects

The nonclinical development programme for Vafseo with the new active substance vadadustat followed relevant ICH guidelines. The pivotal safety studies were performed in compliance with GLP regulations.

4.1 Pharmacology

In time-resolved fluorescence energy transfer (TR-FRET) assays, vadadustat inhibited the three major human hypoxia-inducible factor prolyl-4-hydroxylase domain (HIF-PHD) enzyme isoforms, PHD1, PHD2, and PHD3 with IC_{50} values of 15.41, 11.91, and 7.63 nM, respectively. In the same assay, the metabolites vadadustat-O-glucuronide and glycine-cleaved metabolite of vadadustat, were less potent and are therefore not expected to contribute to the pharmacological activity.

In human hepatoma cells (Hep3B) and umbilical vein endothelial cells (HUVEC), vadadustat showed potent stimulation of HIF-α and erythropoietin (EPO) expression, consistent with PHD inhibition.

In vivo, the efficacy of vadadustat on red blood cell production was demonstrated in mice and rats following repeated oral administration. Vadadustat induced an erythropoietic response, resulting in increases in haematology parameters (e.g. haematocrit and haemoglobin), increased spleen weight, and splenic extramedullary haematopoiesis. In both species, administration of vadadustat resulted in EPO secretion consistent with the proposed mechanism of PHD inhibition, and no effects on vascular endothelial growth factor (VEGF) secretion were observed in rats.

Secondary pharmacodynamic studies with vadadustat revealed a low off-target potential.

Safety pharmacology studies with vadadustat did not reveal a risk for effects on cardiovascular, respiratory, central nervous or renal/urinary system function.

4.2 Pharmacokinetics

In rats and dogs, oral absorption was rapid with peak plasma concentrations reached within 1 to 2 hours after dosing. Oral bioavailability was > 90% in both species. Elimination half-lives were 0.5-2 hours in rats and 2-5 hours in dogs. The pharmacokinetics in the animal species is comparable to that in human (T_{max} 2-3 hours, $t_{1/2}$ 4.5 hours). Following repeated daily dosing, exposure to vadadustat generally increased in a more than proportional manner in rats and dogs. No apparent accumulation was noted in either species, but exposure of vadadustat was somewhat higher in females compared to males.

In vitro plasma protein binding of vadadustat was higher in humans (≥ 99.5%) than in nonclinical species (≥ 93.2%).

In rats and dogs, ^{14}C-vadadustat-related radioactivity was rapidly and widely distributed throughout tissues (T_{max} 2 hours postdose), crossed the blood-brain barrier and the blood-placental barrier, and was excreted into milk. The majority of the radioactivity was found in the faeces (> 80% in both species). In nonclinical species, the major route of elimination of vadadustat and its metabolite is via hepatobiliary elimination into faeces, whereas urinary excretion is the primary route of elimination in humans. The extent of urinary excretion of unchanged vadadustat is reasonably comparable across species.

The *in vitro* metabolism of vadadustat was investigated in liver microsomes and/or hepatocytes of mice, rats, rabbits, dogs, monkeys, and humans. The *in vitro* metabolic turnover of vadadustat was low, and no human-specific metabolites were identified. *In vivo*, vadadustat was extensively metabolised in rats, with the parent vadadustat and the glycine-cleaved metabolite of vadadustat being the most prominent entities in plasma. In dogs, the most abundant radiolabelled components in plasma were vadadustat, the glycine-cleaved metabolite of vadadustat and vadadustat-O-glucuronide. Vadadustat-O-glucuronide is the only major metabolite in humans, and sufficient exposure was demonstrated in the pivotal repeat-dose toxicity and reproductive studies. The acyl-glucuronide, which was detected in mice and rats, was identified in humans as a minor metabolite (< 1% total vadadustat exposure) and does not raise safety concerns.

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4.3 Toxicology

The toxicological profile of vadadustat was evaluated in mice, rats, rabbits, and dogs. The selection of rat and dog as species for toxicological assessment is considered appropriate as the metabolism, pharmacodynamic effects, and pharmacokinetic profile of vadadustat are comparable in both species and humans. The oral route of administration and frequency of dosing (once daily) in the nonclinical studies are consistent with the proposed clinical setting.

Pivotal repeat-dose toxicity studies were conducted up to 26 weeks in rats at doses of 0, 20, 40 or 60 mg/kg/day and 39 weeks in dogs at doses of 0, 10, 25 or 50 mg/kg/day.

Pharmacology-related effects, including increase in red blood cells (RBC) mass (RBC count, haemoglobin concentration, haematocrit) and reticulocyte counts with pathology correlates were observed at ≥ 40 mg/kg/day in rats and 50 mg/kg/day in dogs. Administration of vadadustat in the non-anaemic healthy animals induced mortalities. The cause of death or moribundity was considered related to the exaggerated pharmacology of vadadustat that increased blood viscosity leading to hemodynamic changes and reduced perfusion (ischaemia).

The main target organs were the haematopoietic system, heart, and stomach in rats, and adrenal glands in dogs. Vadadustat-related increased extramedullary haematopoiesis in the spleen was associated with clinical pathology changes, enlarged spleen, increased spleen weight, and increased cellularity of the bone marrow. Heart valve findings (stromal proliferation, thrombus, haemorrhages, and inflammatory cell infiltration) observed at high doses (≥ 60 mg/kg/day) and glandular stomach changes (including haemorrhage, necrosis, congestion, oedema, and/or fibrin thrombosis) at ≥ 40 mg/kg/day were considered to be associated with polycythaemia and secondary to the exaggerated pharmacology of vadadustat. The non-proliferative infiltration of mononuclear cells with aggregation of hypertrophied cells in the adrenal gland cortex of dogs was not associated with clinical signs or clinical chemistry changes. All findings were reversible or showed a tendency to reversibility following 12-week recovery periods. Although the transition between the pharmacological effect of vadadustat and toxicity characterised by the adverse findings is fluid, these changes are considered of low risk, since polycythaemia can be monitored and controlled in the clinic by titration of the dose according to therapeutic haemoglobin criteria. However, thromboembolic events are considered to be an important potential risk in patients. The change in the adrenal gland in dogs is considered non-adverse. There were no safety margins at the NOAELs for systemic toxicity in the chronic toxicity studies in rats (26-week) and in dogs (39-week), corresponding to 0.47 and 0.086 times the human exposure based on AUC at the MRHD of 600 mg.

Vadadustat was negative in genotoxic assays conducted according to ICH S2 (R1).

Vadadustat was not carcinogenic in rats or transgenic mice. The maximum doses used in the studies (20 mg/kg/day in rats and 50 mg/kg/day in mice) were associated with a plasma exposure below the clinical exposure at the highest recommended dose of 600 mg/day. Therefore, with regard to the long-term clinical dosing of vadadustat, a risk of potential carcinogenicity cannot be excluded as HIF regulates multiple aspects of tumorigenesis and renal cancer has been associated with deregulation of hypoxia signalling pathways.

Fertility parameters were not affected in male and female rats. In the studies on embryofetal development and pre-/postnatal development no teratogenicity was observed up to the highest doses, associated with exposures below the clinical AUC at the highest recommended dose of 600 mg/day. Developmental effects were noted only in the rat at dose levels corresponding to 1.7 times the human exposure at the 600 mg dose, specifically a decrease in fetal body weight and reduced skeletal ossification, both of which were considered secondary to maternal toxicity. This is adequately reflected in the information for healthcare professionals.

Although the current application is for adult patients, a juvenile animal toxicity study was conducted in accordance with the EMA PIP. Rats were treated orally with up to 40 mg/kg/day from postnatal day (PND) 7 to PND 27, followed by dosing up to 80 mg/kg/day from PND 28 to PND 76. There was no evidence that juvenile rats were more sensitive to vadadustat compared to adult rats.

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Vadadustat was negative for phototoxicity *in vivo* in pigmented rats.

The Nonclinical Safety Specifications in the RMP adequately address the nonclinical findings and their relevance for clinical use.

Impurities are controlled according to ICH Q3A/B and ICH M7. There are no concerns about excipients.

Based on the ERA, the risk for the environment is low.

4.4 Nonclinical conclusions

In conclusion, the nonclinical documentation is sufficient to support the approval of Vafseo (vadadustat) in the proposed indication. The pharmacodynamic studies and the safety programme do not suggest any particular adverse effects in patients. All nonclinical data relevant to safety are mentioned in the information for healthcare professionals. From the nonclinical perspective, approval may be granted in the proposed indication.

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5 Clinical and clinical pharmacology aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Vafseo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼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 new or serious adverse reactions. See "Undesirable effects" for advice on the reporting of adverse reactions.

VAFSEO

Composition

Active substances

Vadadustat

Excipients

Tablet core: microcrystalline cellulose, sodium carboxymethyl starch (Type A) (sodium content between 0.38 to 1.74 mg/film-coated tablet), hypromellose, colloidal silicon dioxide, magnesium stearate
Tablet coating: polyvinyl alcohol, macrogol 3350, talc, titanium dioxide – E171, yellow iron oxide – E172 (300 mg tablets only), red iron oxide– E172 (450 mg tablets only) and black iron oxide (450 mg tablets only).

Each 150 mg film-coated tablet contains 0.38 to 0.58 mg sodium.
Each 300 mg film-coated tablet contains 0.77 to 1.15 mg sodium.
Each 450 mg film-coated tablet contains 1.16 to 1.74 mg sodium.

Pharmaceutical form and active substance quantity per unit

Vafseo 150 mg film-coated tablets: Each 150 mg film-coated tablet contains 150 mg of vadadustat. Round, white tablets debossed with “VDT” on one side and “150” on the other side.
Vafseo 300 mg film-coated tablets: Each 300 mg film-coated tablet contains 300 mg of vadadustat. Oval, yellow tablets debossed with “VDT” on one side and “300” on the other side.
Vafseo 450 mg film-coated tablets: Each 450 mg film-coated tablet contains 450 mg of vadadustat. Oval, pink tablets debossed with “VDT” on one side and “450” on the other side.

Indications/Uses

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

Dosage/Administration

Initiation of treatment

Chronic dialysis-dependent patients who are already being treated with an erythropoiesis-stimulating agent (ESA) should be initially switched from their ESA treatment to treatment with Vafseo. The recommended starting dose of Vafseo in this case is 300 mg daily, regardless of the previous ESA dosage. For patients who have not received prior treatment with an ESA, the starting dose is likewise 300 mg once daily.

When switching from an ESA to Vafseo, haemoglobin (Hb) values may fall initially (particularly in patients who have previously been treated with an ESA at a high dose) but then gradually return to baseline typically by Week 16-20 (see “Pharmacodynamics” regarding the development of Hb values during treatment in individual studies).

Treatment with Vafseo should be discontinued if a clinically significant increase in Hb value has not been achieved with 24 weeks of initiating treatment. It may only be resumed if the reasons for the lack of response have been fully investigated, have not been shown to constitute a basic restriction for the use of Vafseo, and have been adequately treated. Otherwise an alternative treatment must be found for the long-term.

If the initial response is insufficient (e.g. Hb drops below 9.0 g/dL), rescue therapy in the form of RBC transfusions or treatment with an ESA should be considered (see “Warnings and precautions”).

It is recommended that treatment with Vafseo be continued in patients receiving RBC transfusions. In patients receiving temporary rescue therapy with an ESA, treatment with Vafseo should be interrupted and then resumed only when the Hb level has increased to values ≥10g/dL. In such cases, Vafseo treatment should be interrupted for the periods stated below in Table 1, following administration of the final dose of the respective ESA.

Table 1: Interruption period for patients receiving ESA

ESA	**Time of interruption of Vafseo treatment**
Epoetin	2 days
Darbepoetin alfa	7 days
Methoxy polyethylene glycol-epoetin beta	14 days

Following rescue therapy, Vafseo treatment should be resumed at the original or higher dose. In doing so, and during further dose titration, the following guidelines should be followed.

Dose titration based on Hb monitoring: In order to achieve and maintain Hb values of ≥10 g/dL to ≤12 g/dL, the dose can be adjusted in increments of 150 mg within the range of 150 mg to 600 mg (the maximum recommended daily dose) according to the algorithm described in Table 2. Following initiation of treatment with Vafseo and each dosage adjustment, Hb values should be checked every two weeks until stable, then at least once monthly thereafter. The dose must not be increased more frequently than once every 4 weeks; dose reductions can occur at shorter intervals.

Table 2: 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 treatment with Vafseo until Hb level has decreased to ≤12 g/dL. Resume treatment at a dose reduced by 150 mg (compared with the dose before treatment interruption). If the dose before treatment interruption was 150 mg, then resume treatment at a dose of 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 of liver function

Before initiation of treatment with Vafseo and for at least the following three months, ALT, AST and bilirubin values must be checked monthly, then as clinically indicated thereafter (see “Warnings and precautions”).

Other 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 and 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 “Interactions”).

Other causes of anaemia

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

Special dosage instructions

Patients with renal disorders

No dose adjustment is needed in patients with renal impairment (see “Pharmacokinetics”).

Patients with hepatic disorders

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 ”Warnings and precautions” and “Pharmacokinetics”).

Elderly patients

No dose adjustment is recommended for elderly patients (see “Pharmacokinetics”).

Children and adolescents

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

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.

Mode 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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.

Warnings and precautions

The efficacy of vadadustat (see "Mechanism of action”) is based on stimulation of the transcription of genes regulated by hypoxia-inducible factor (HIF). This includes genes with known undesirable effects. The potential risks (e.g. malignancy) associated with vadadustat therapy cannot currently be fully and definitively assessed.

Cardiovascular and mortality risk

Controlled clinical trials in dialysis-dependent patients with CKD (DD-CKD) showed a comparable risk of serious cardiovascular events (all-cause mortality, non-fatal stroke or non-fatal myocardial infarction [MI]) for treatment with Vafseo and darbepoetin alfa, respectively. However, in similar trials, non-dialysis-dependent CKD patients (NDD-CKD) on treatment with Vafseo showed an increased risk of serious cardiovascular events (see “Undesirable effects”) compared with treatment with darbepoetin alfa. Due to this increased risk, NDD-CKD patients should not be treated with Vafseo. Regardless of dialysis status, signs and symptoms of serious adverse cardiovascular events should be immediately and carefully investigated and the treatment of the affected patient should be adjusted according to an individual risk-benefit assessment.

Thromboembolic events

In two active controlled clinical trials of DD-CKD, thromboembolic events such as vascular access thrombosis (VAT) (arteriovenous graft thrombosis and arteriovenous fistula thrombosis) were reported as very common in patients treated with Vafseo (see “Undesirable effects”). VAT presents a general risk for patients on haemodialysis. Therefore, when the patient presents risk factors for thromboembolic events, including a history of deep vein thrombosis, pulmonary embolism or stroke, treatment should be preceded by careful assessment of the individual risk-benefit ratio and treatment should be monitored accordingly. Patients with signs and symptoms of thromboembolic events must be evaluated immediately and treated accordingly. Potential discontinuation of Vafseo treatment should be considered. An overly rapid or excessive increase in Hb value (>1 g/dL within 2 weeks) can increase the risk of thromboembolic events. In order to prevent this, the dose adjustments described in “Dosage/Administration” must be implemented meticulously.

Hepatic impairment

Vafseo is not recommended for use in patients with severe hepatic impairment (Child-Pugh class C) (see “Properties/Effects”).

Hepatotoxicity

An increase in ALT, AST (frequency common) and/or bilirubin (frequency uncommon) attributed to Vafseo was reported (see “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 “Dosage/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 “Dosage/Administration” and “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 “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 practice. Patients should be advised on the importance to comply with antihypertensive therapy and monitoring of blood pressure.

Seizures

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

Initial decrease in Hb levels in patients converting from ESA

Hb levels may initially decrease when converting patients from an ESA to Vafseo especially in patients who were on high baseline ESA doses. Generally, the higher the baseline ESA dose, the deeper the initial decrease in Hb levels will be before levels gradually return to baseline Hb by Weeks 16 to 20 (see “Pharmacodynamics” 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 “Dosage/Administration” and “Properties Effects”).

Malignancy

Persistently increased transcription of HIF-regulated genes is potentially associated with undesirable effects on the growth of solid tumours. Preclinical studies do not allow explicit conclusions (see "Preclinical Data"). Vadadustat has not been studied in patients with malignant disease. Use in patients with malignant disease is not recommended.

Retinopathy

Exacerbation of retinopathy is a potential safety risk of treatment with Vafseo, as, due to its mechanism of action, Vafseo can stimulate retinal angiogenesis. Study data have not established a more frequent occurrence of retinopathy on treatment with Vafseo in comparison with darbepoetin alfa; however, a conclusive evaluation was not possible as the studies performed had not included a sufficient number of at-risk patients. Treatment of patients with pre-existing retinopathy should be considered carefully. Patients should be examined by an ophthalmologist immediately if they experience visual disturbances.

Use in patients with polycystic kidney disease

In patients with polycystic kidney disease, high-grade hypoxia causes chronic activation of HIF-1a in the cyst epithelium and peritubular interstitium, which evidently further stimulates cyst growth. There are no safety data available for vadadustat in patients with polycystic kidney disease. Treatment of patients with polycystic kidney disease should be considered carefully and implemented only with close monitoring of cyst size.

Abuse

Abuse can lead to an excessive rise in Hb and life-threatening cardiovascular complications.

Sodium

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

Interactions

Effect of other agents on the pharmacokinetics of vadadustat

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

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

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

Organic anion transporter (OAT) OAT1/OAT3 inhibitors

Co-administration with probenecid, an OAT1/OAT3 inhibitor, increased vadadustat AUC values almost 2-fold. If co-administration with strong or moderate OAT1 or OAT3 inhibitors (e.g. benzylpenicillin, teriflunomide or p-aminohippuric acid) occurs, patients should be managed cautiously

and evaluated for excessive effects of vadadustat. For potential adverse reactions and dose adjustment in case of rapid Hb rise please refer to “Undesirable effects” and “Dosage/Administration”.

Effect of vadadustat on the pharmacokinetics of other medicinal products

Concomitant use contraindicated: none

CYP2B6 substrates:

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

CYP2C9 *substrates*

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

CYP3A4 substrates

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

CYP2C8 substrates

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

Other interactions

BCRP substrates and some statins
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 3):

Table 3: 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 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_{max}	Consider limiting the dose of rosuvastatin in CKD patients on Vafseo to 10 mg daily. Monitor for signs of adverse effects of rosuvastatin.

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

OAT3 substrates

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

Dose adjustment of concomitantly administered OAT3 substrate may be needed.

Pregnancy, 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 “Preclinical data”). As a precautionary measure, use of Vafseo during pregnancy should be avoided.

Breast feeding

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

Fertility

No data are available on the effect of vadadustat exposure on human fertility. Studies in animals showed no effects of vadadustat on fertility (see “Preclinical data”). The potential risk for humans is unknown.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The adverse reactions are based on pooled data from four active-controlled studies in DD-CKD and NDD-CKD of 3686 patients treated with vadadustat and 3687 treated with darbepoetin alfa, including 2923 exposed for at least 6 months and 2011 exposed for greater than one year to vadadustat. The population for vadadustat was 19 to 104 years of age, 51.2% male, and the percentage of Caucasian, Hispanic, Black (including African Americans) and Asian patients was 66%, 35.6%, 20.3%, and 5.4%, respectively.
The most frequent adverse reactions in DD-CKD and NDD-CKD patients treated with vadadustat respectively were hypertension (11.1% / 16.0%), diarrhoea (12.7% / 13.9%) and thromboembolic events (13.7% / 6.9%).
Due to the study design (active comparator darbepoetin) it cannot be ruled out that Vafseo has other adverse drug reactions (ADRs) compared to placebo. This primarily concerns the ADRs known for ESAs (such as tumours). Interpretation of a comparable (or only slightly lower) incidence of these ADRs in vadadustat-treated patients (vs. darbepoetin-treated) must be made with caution.

Tabulated list of adverse reactions

All ADRs are listed by system organ class (SOC) and frequency:
"very common" (≥1/10); "common" (≥1/100, <1/10); "uncommon" (≥1/1’000, <1/100); "rare" (≥1/10’000, <1/ 1’000); "very rare" (<1/10’000); "not known" (frequency cannot be estimated from the

available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

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

[a] For further details please refer to “Thromboembolic events” and “Seizures” below

[b] Includes preferred terms transaminases increased, ALT increased, AST increased, hepatic enzyme increased, liver function test abnormal

Description of selected adverse reactions

Thromboembolic events

Cerebrovascular accident events occurred in 0.8% vs 0.9% (0.5 vs 0.5 events/100 PY) of the DD-CKD population; and in 0.9% vs 1.0% (0.6 vs 0.6 events/100 patient years [PY]) of the NDD-CKD population; in the vadadustat and the darbepoetin alfa groups respectively.

Deep vein thrombosis (DVT) events occurred in 0.7% vs 0.5% (0.4 vs 0.3 events/100 PY) of the DD-CKD population; and in 0.9% vs 1.3% (0.5 vs 0.7 events/100 PY) of the NDD-CKD population; in the vadadustat and darbepoetin alfa groups respectively.

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

Transient ischaemic attack events occurred in 0.8% vs 0.4% (0.5 vs 0.3 events/100 PY) of the DD-CKD population; and in 0.8% vs 0.4% (0.4 vs 0.3 events/100 PY) of the NDD-CKD population; 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 PY) of the DD-CKD population and in 4.0% vs 3.1% (2.3 vs 1.9 events/100 PY) of the NDD-CKD population, in the vadadustat and darbepoetin alfa groups respectively.

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

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

For information on cardiovascular and mortality risk and thromboembolism please see “Special warnings and precautions for use” and “Pharmacodynamic properties”.

Cardiovascular safety - dialysis-dependent CKD patients

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. Vadadustat met the composite primary safety endpoint defined as non-inferiority of vadadustat to darbepoetin alfa in time to occurrence of MACE for the global study population (1.3 NI margin [HR (95% CI) was 0.96 (0.83, 1.11)]. The results were consistent for the primary endpoint and the individual components of the primary endpoint (see Table 4). The results for the primary MACE endpoint were also supported by the results from key secondary endpoints using expanded MACE definitions. These results showed that vadadustat did not decrease the time to MACE plus hospitalization for heart failure; MACE plus thromboembolic events excluding vascular access; cardiovascular (CV) MACE (all-cause mortality, non-fatal MI or non-fatal stroke); CV death or all-cause mortality compared to darbepoetin.

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

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

*The MACE analyses were conducted on randomised subjects who received at least 1 dose of study treatment.

CI: confidence interval; MACE: major adverse cardiovascular events.

Cardiovascular safety - non-dialysis-dependent CKD patients

The incidence of MACE was assessed as part of the long-term safety evaluation of the two global efficacy studies in NDD-CKD patients. Vadadustat did not meet the composite primary safety endpoint defined as non-inferiority of vadadustat to darbepoetin alfa in time to first occurrence of MACE (all-cause mortality, non-fatal MI or non-fatal stroke) for the global study population. The HR (95% CI) was 1.17 (1.012, 1.36) with the upper bound exceeding the pre-specified non-inferiority margin of 1.3 (see Table 5) . The difference between the two treatments with respect to MACE (38 patients or 2.1%) was driven primarily by non-fatal MI (22 patients (1.3%)) and all-cause mortality (10 patients (0.5%)).

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

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

Non-fatal stroke	32 (1.8)	26 (1.5)	

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

Elevated liver enzymes and blood bilirubin increased:

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

In NDD-CKD patients, seizures occurred in 0.7% (0.4 patients with events per 100 PY of exposure) in the vadadustat group, and 0.8% (0.5 patients with events per 100 PY of exposure) in the darbepoetin alfa group (see "Warning and precautions").
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

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

Treatment

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.

Properties/Effects

ATC code

B03XA08; Anti-anaemic preparations, other anti-anaemic preparations.

Mechanism of action

Vadadustat stabilises hypoxia-inducible factor (HIF) by inhibiting prolyl hydroxylases involved in transcription factor degradation (PH1, PH2, PH3). Ultimately, the resultant intracellular accumulation and nuclear translocation of HIF-α mediate an increase in the transcription of HIF-regulated genes. Among other things, endogenous erythropoietin (EPO) production is stimulated, thereby increasing iron mobilization and red blood cell production, resulting in a gradual rate of rise in Hb (see Figures 1 and 2).

Pharmacodynamics

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

Cardiac electrophysiology

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

Clinical efficacy

The efficacy and safety of vadadustat given once daily for the treatment of anaemia in adult patients with CKD was demonstrated compared to darbepoetin alfa in global multi-centre, randomised, active-controlled, non-inferiority, open-label studies of 3923 DD patients and 3476 NDD patients.
Patients with diagnosis of NDD-CKD with an eGFR > 60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation at screening were excluded from pivotal studies.

Patients were randomised 1:1 to receive vadadustat with a starting dose of 300 mg once daily or darbepoetin alfa administered subcutaneously or intravenously as per prescribing information for 52 weeks to assess the efficacy endpoints. Vadadustat was titrated in increments of 150 mg up to 600 mg to achieve the patient's Hb target. After 52 weeks, patients were continued study treatment to assess long-term safety until the event-driven 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 or non-fatal stroke.

Treatment of anaemia in dialysis-dependent patients

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 ESA-naive, 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, vadadustat was non-inferior to darbepoetin alfa in correcting and maintaining or maintaining Hb levels across geographic-specific target Hb ranges [10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL in Europe and rest of world (ROW)] at weeks 24 to 36 and weeks 40 to 52 in adult DD-CKD patients with anaemia. Results for the primary and secondary efficacy endpoints are provided in Table 6. 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 6: INNO$_2$VATE STUDIES

	INNO$_2$VATE 1		INNO$_2$VATE 2	
Hb (g/dL)	**Vadadustat N = 181**	**Darbepoetin alfa N = 188**	**Vadadustat N = 1777**	**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]
Estimated treatment difference [95% CI] vadadustat – darbepoetin Alfa	-0.31 [-0.53, -0.10]		-0.17 [-0.23, -0.10]	
Key secondary endpoint Weeks 40 to 52 mean (SD)	10.51 (1.19)	10.55 (1.14)	10.40 (1.04)	10.58 (0.98)
Adjusted mean change from baseline (LSM) [95% CI]	1.42 [1.17, 1.68]	1.50 [1.23, 1.76]	0.23 [0.16, 0.29]	0.41 [0.34, 0.48]
Estimated treatment difference [95% CI] vadadustat – darbepoetin alfa	-0.07 [-0.34, 0.19]		-0.18 [-0.25, -0.12]	

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

Figure1: Mean (+/-SD) of change from baseline in Hb (g/dL) for INNO$_2$VATE 1 incident dialysis

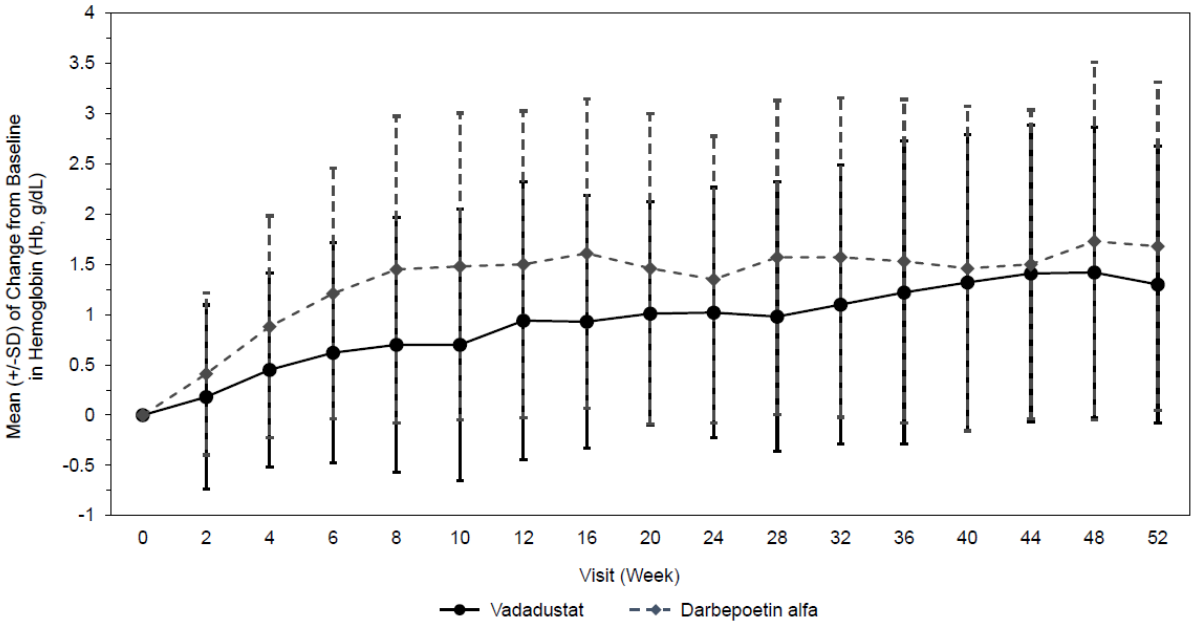
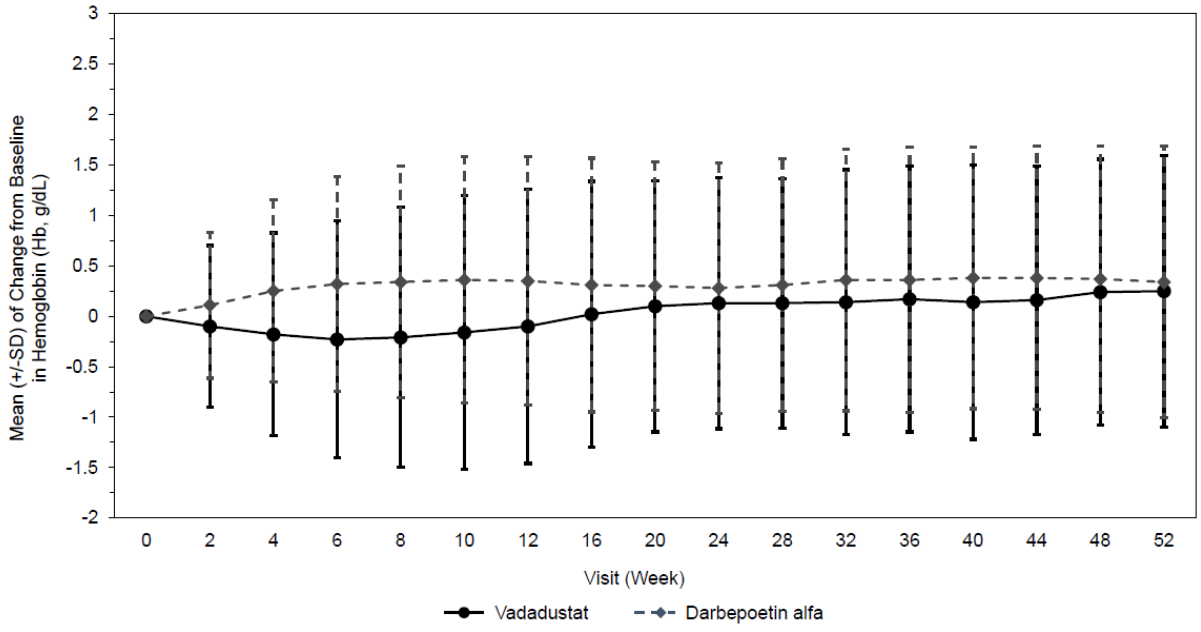


Figure2: Mean (+/-SD) of change from baseline in Hb (g/dL) for INNO$_2$VATE 2 prevalent dialysis



Pharmacokinetics

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.

Elimination

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

Linearity/non-linearity

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

Kinetics in specific patient groups

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).

Renal impairment

Vadadustat clearance decreased with decreasing estimated glomerular filtration rate (eGFR) in NDD-CKD patients and exposures in dialysis patients were approximately 2-fold higher compared to healthy subjects. In patients with Stage 5 DD-CKD, no significant differences in pharmacokinetics (C_{max}, AUC or mean half-life) were observed when vadadustat was administered 4 hours before dialysis or 2 hours after dialysis.

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.

Preclinical data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity.

Repeat dose toxicity

In non-clinical studies, mortalities were observed in mice, rats, rabbits and dogs 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).

Carcinogenicity

Long-term carcinogenicity studies in rats (duration of 2 years) and transgenic rasH2 mice (duration of 6 months) showed no evidence of carcinogenic potential (no treatment-related tumours) at the highest vadadustat doses tested. However, the exposure (AUC) in rats and mice was below the maximum human exposure (MRHD) of 600 mg/kg, and consequently a risk of malignancy cannot be excluded and at present the clinical significance remains unclear.

Reproductive toxicity

Embryofetal development toxicity studies show that vadadustat administered to pregnant rats and rabbits was not teratogenic in either species up to the highest dose level tested, corresponding to 1.7

and 0.16 times the human exposure at the 600 mg dose (based on the AUC at the MRHD in NDD-CKD patients). Mild development effects were noted only in the rat at dose levels corresponding to 1.7 times the human exposure at a dose of 600 mg ; characterised as a 6-7% decrease in fetal body weight and an increased incidence of reduced skeletal ossification, both of which were considered secondary to the decline in body weight and food consumption in the pregnant dams. 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 fetal body weight at 240 mg/kg/day, but no teratogenicity.
Fertility and early embryonic development and prenatal and postnatal development reproduction toxicity studies were conducted in female and male rats at dose levels of 40 to 120 mg/kg/day. In these studies, vadadustat did not impact fertility or development of offspring.

Toxicity tests with juvenile animals

A 10-week juvenile toxicity study in rats with doses of 5 to 80 mg/kg/day did not reveal any new safety findings to that already observed in adult rats after repeat dosing with vadadustat.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.

Authorisation number

68862

Packs

Vafseo 150 mg

Pack with 28 film-coated tablets, 2 blisters [A]
Pack with 98 film-coated tablets, 7 blisters [A]

Vafseo 300 mg

Pack with 28 film-coated tablets, 2 blisters [A]
Pack with 98 film-coated tablets, 7 blisters [A]

Vafseo 450 mg

Pack with 28 film-coated tablets, 2 blisters [A]
Pack with 98 film-coated tablets, 7 blisters [A]

Marketing authorisation holder

Voisin Consulting CH Sàrl; 1015 Lausanne

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