Difference of LSM (SE)	0.1449 (0.1400)
95% Confidence Interval	-0.1304 ,0.4202 (p Value- 0.3014)
Lower margin of 95% CI of difference of LSM (SE) is less than -1 g/dL- **Non-inferiority achieved.**	

5.3 Pharmacokinetic properties

Study in pre dialysis patients:
Desidustat was administered orally once every other day (alternate-day dosing) for 6 weeks at three dose levels (100, 150, 200 mg) in pre dialysis chronic kidney disease patients (n=11/ dose): the exposure (C_{max} and AUC_{0-t}) of desidustat was increased in dose-related manner from 100 to 200 mg dose, no drug accumulation following a multiple doses and mean elimination half-life was ranged from 6 to 14 h.

Study in dialysis patients
A single oral dose of desidustat was administered in dialysis chronic kidney disease patients at three dose levels (50, 100, 150 mg, n=8/dose) within 2 h of dialysis. The time to achieve peak blood concentration was observed at about 2.5 h post dosing, the exposure (C_{max} and AUC_{0-t}) was increased at 50 and 100 mg dose, the geometric mean elimination half-life was ranged from 6-15 h.

Absorption
Following single dose oral administration at 50 mg in healthy human under the fasting condition, the time to achieve peak blood concentration (median T_{max}) was about 1.3 h and mean elimination half-life was about 8.7 h. Food delayed the time to reach peak blood levels (T_{max}), reduced C_{max} and exposure (AUC_{0-t}).

Distribution
In vitro study revealed that desidustat was highly bound to plasma protein (about 99%) and is not preferentially distributed in erythrocytes.

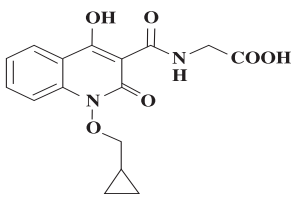
Metabolism
Desidustat was metabolically stable when incubated with human liver microsomes, human hepatocytes or recombinant human CYP isoforms. In vivo, two minor metabolites (<10%) were identified one represented hydroxylation and another hydroxyl-glucuronide in clinical pharmacology (non-radiolabeled) study. Desidustat did not show potential to form reactive GSH adduct.

Excretion
Following a single oral dose administration in healthy adult male subjects with an empty stomach, the urinary excretion of unchanged desidustat was about 27 to 41% across the tested dose range (10 to 300 mg). The minor metabolites, hydroxylated and hydroxyl-glucuronide metabolites were also excreted in human urine (non-radiolabel study).

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology
Carcinogenesis: No evidence of carcinogenicity was noticed in rats following oral administration of Desidustat for a duration of 2 years at doses up to 20 mg/kg in males and 30 mg/kg in females (approximately 1-2 times the MRHD for treating anemia in patients with chronic kidney disease on mg/kg basis).
Mutagenesis: Desidustat did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Desidustat was not mutagenic in the Ames test and did not increase chromosomal aberrations in human lymphocytes *in vitro* or in mice bone marrow *in vivo*.
Impairment of Fertility: No adverse effects on male or female fertility were identified in rats administered Desidustat orally at doses up to 30 mg/kg (2 times the MRHD for treating anemia in patients with chronic kidney disease on mg/kg basis) prior to and during mating and early pregnancy.

7. Description
Desidustat is a prolyl hydroxylase domain (PHD) inhibitor. The chemical name for Desidustat is N-[[1-(cyclopropylmethoxy)-1,2-dihydro-4-hydroxy-2-oxo-3-quinolinyl]carbonyl]-glycine
OR
Glycine, N-[[1-(cyclopropylmethoxy)-1,2-dihydro-4- hydroxy-2-oxo-3-quinolinyl]carbonyl]-
Figure 1: Structural formula of Desidustat



The empirical formula of Desidustat is $C_{16}H_{16}N_2O_6$ and the molecular mass is 332.31 g/mol.

8. Pharmaceutical particulars

8.1 Incompatibilities
There is no known incompatibilities of Desidustat Tablets.

8.2 Shelf-life
24 Months

8.3 Packaging information
Desidustat is available as uncoated tablets for oral administration. Desidustat Tablets are supplied in blister pack.

8.4 Storage and handing instructions
Store below 30°C. Keep out of reach of children.

9. Patient Counselling Information
- Do not use Desidustat tablet for a condition for which it was not prescribed.
- Do not consume any food 01 hour before and 02 hours after taking Desidustat.
- Do not give Desidustat tablet to other people, even if they have the same symptoms you have.

Contact your healthcare provider if you develop any symptoms after consumption of Desidustat.

10. Details of manufacturer
Manufactured by: **Zydus Lifesciences Limited**
Survey No. 417, 419 and 420, Sarkhej Bavla National Highway No. 8A,
Village-Moraiya, Tal-Sanand, Dist-Ahmedabad - 382 210

11. Details of permission or license number
Mfg. Lic. No.: G/25/1486

12. Date of revision
16/07/2024

zydus

Marketed by: **Zydus Lifesciences Limited**

To report adverse events, call toll free on
1800 419 1141 or visit www.zyduslife.com

Simply send an email at: drugsafety@zyduslife.com

® Registered Trademark

2098502

1. Generic Name

Desidustat Tablets 100 mg

Oxemia® 100

2. Qualitative and quantitative composition

Each uncoated tablet contains:

Desidustat	100 mg
Excipients	q.s.

Inactive ingredients in the tablet are microcrystalline cellulose, lactose, croscarmellose sodium, hypromellose, talc and magnesium stearate.

3. Dosage form and strength
Desidustat is available as uncoated tables for oral administration.
Each uncoated tablet contains 100 mg of Desidustat.

4. Clinical particulars

4.1 Therapeutic indication
Desidustat is indicated for the treatment of
- Anemia in Adult Patients with Chronic Kidney Disease (CKD) not on Dialysis and on Dialysis

4.2 Posology and method of administration

Do not consume any food 01 hour before and 02 hours after taking Desidustat.

For Non-Dialysis Patients
- The starting dose of Desidustat is 100 mg (4 tablets of 25 mg OR 2 tablets of 50 mg OR 1 tablet of 100 mg) orally thrice in a week [Dosing will be done 2 days apart (eg-Monday, Wednesday, Friday or Tuesday, Thursday, Saturday) but not 4 days apart]. The dose should be then adjusted according to the patient's Hemoglobin level every 4 weeks as per table 1. However, the maximum dose should not exceed 150 mg thrice in a week.

For Dialysis Patients,
- The Starting dose of Desidustat is 100 mg (4 tablets of 25 mg OR 2 tablets of 50 mg OR 1 tablet of 100 mg) or 125 mg (5 tablets of 25 mg OR 2 tablets of 50 mg and 1 tablet of 25 mg OR 1 tablet of 100 mg and 1 tablet of 25 mg) or 150 mg (6 tablets of 25 mg OR 3 tablets of 50 mg OR 1 tablet of 100 mg and 1 tablet of 50mg) thrice in a week [Dosing will be done 2 days apart (eg-Monday, Wednesday, Friday or Tuesday, Thursday, Saturday) but not 4 days apart] depending upon the previous Epoetin/Darbepoetin/ Methoxy polyethylene glycol-epoetin beta dose. The Starting dose for new patients is 100 mg orally thrice in a week. The dose should be then adjusted according to the patient's Hemoglobin level every 4 weeks. However, the maximum dose should not exceed 150 mg thrice in a week.
- It is recommended that Desidustat is to be taken after completion of the dialysis session.

Table 1: Dose adjustments rules.

Change in Hb g% level every 4 weeks	Hb<10 g%	Hb 10 to <11 g%	Hb 11 to <12 g%	Hb ≥ 12 g%
<1.0 increase	Increase the dose	Increase the dose	Maintain the dose	Stop the treatment for 14 days, Initiate one lower dose if Hb < 11.5 g%
≥1.0 increase to ≤ 2.0 increase	Maintain the dose	Maintain the dose	Decrease the dose	
>2.0 increase	Maintain the dose	Decrease the dose	Decrease the dose	

Table 2: Starting doses of Desidustat in patients converting from Epoetin/Darbepoetin/Methoxy polyethylene glycol-epoetin beta

Epoetin (IU/week)	Darbepoetin (µg/week)	Methoxy polyethylene glycol-epoetin beta (µg/month)	Desidustat (mg, three time in a week)
<8000	<40	<120	100
8000 to 16000	40-80	120-200	125
>16000	>80	>200	150

4.3 Contraindications
Hypersensitivity to Desidustat or any of the excipients used in the formulation.

4.4 Special warnings and precautions for use
No drug related severe or serious adverse event or any life-threatening condition which requires special attention observed during the study.

4.5 Drugs interactions
The in vitro assays did not reveal any significant inhibition of major drug metabolizing enzymes CYPs 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4/5 (IC50 > 300 µM). Desidustat is also not a time dependent inhibitor of CYP3A4/5. Desidustat was not an inducer of CYP1A2 and CYP3A4 at 100 µM. Based on available data, Desidustat has a minimal potential to cause CYP-mediated clinical drug-drug interaction at therapeutically relevant concentrations in human.
Desidustat was not found to be a substrate for human drug transporters P-gp or BCRP at gastrointestinal pH 5.5. Desidustat did not interact significantly with other human drug transporters such as OATP1B1, OATP1B3, OAT1, OCT2 at 30µM, but it showed interaction with OAT3 (IC50 of 1.7 µM).

4.6 Use in special populations

Pregnancy
The safety of Desidustat in pregnant women has not been established as there is no adequate and well controlled study carried out in pregnant women. Women who become pregnant during Desidustat treatment should contact their physicians. Desidustat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
In animal developmental and reproduction studies, no fetal toxicity or maternal toxicity or evidence of malformations in fetus was noticed in pregnant rabbits up to 135 mg/kg after Desidustat administration by oral route. In pregnant rats, no embryofetal toxicity was noticed up to 60 mg/kg but delayed (incomplete) ossification of caudal vertebrae and unossified sternebrae in fetus was noticed at 120 mg/kg. No maternal toxicity and malformations in fetus in rats was noticed up to 120 mg/kg. When Desidustat was given orally to pregnant or lactating female rats, no adverse effects was noticed in the development of conceptus and post-natal parameters up to 30 mg/kg, however fertility index of F1 generation was low at 30 mg/kg. The NOAEL of pre- and post-natal development study was considered to be 15 mg/kg in rats.

Nursing mothers
Nursing mothers should not use Desidustat because it is not known whether Desidustat is excreted into the breast milk.

Women with childbearing potential
Women with childbearing potential should use appropriate contraceptive method during treatment.

Pediatric use
Safety and efficacy of Desidustat in pediatric patients have not been established.

Geriatric use
Considering the comorbidity and concomitant medications in elderly patients, Desidustat should be used with caution in geriatric patients.

4.7 Effects on ability to drive and use machines
Desidustat does not have any influence on the ability to drive and use machines.

4.8 Undesirable effects
Adverse events reported from Phase-III Studies
Study: DESI.18.001 (DREAM-ND)
A phase III, open label and comparative study on 588 anaemic CKD patients not dependent on dialysis comparing Efficacy and safety of Desidustat tablet with Darbepoetin injection revealed that a total of 642 adverse event in 289 subjects (288 AEs in Desidustat arm and 354 in Darbepoetin alfa arm) were reported during 24 weeks treatment period. In total, 283 (48.13%) subjects had at

least one TEAE during the treatment period: 137 (46.60%) subjects in the Desidustat treatment group and 146 (49.66%) subjects in the Darbepoetin treatment group. The most frequently reported TEAEs (reported in ≥ 2% of subjects in the either of the treatment groups) is presented in table 3.

Table 3: TEAEs reported in ≥ 2% of subjects in Desidustat and Darbepoetin alfa up to week 24

AE term	Desidustat Oral Tablet (N = 294) n (%)	Darbepoetin Alfa Injection (N = 294) n (%)
Number of Subjects with at least one TEAE	137 (46.60)	146 (49.66)
Abdominal pain	5 (1.70)	9 (3.06)
Gastritis	2 (0.68)	7 (2.38)
Constipation	8 (2.72)	5 (1.70)
Vomiting	10 (3.4)	10 (3.4)
Asthenia	9 (3.06)	10 (3.4)
Injection site reaction	0 (0.0)	7 (2.38)
Oedema	8 (2.72)	5 (1.70)
Peripheral oedema	16 (5.44)	9 (3.06)
Pain	6 (2.04)	12 (4.08)
Pyrexia	20 (6.80)	20 (6.80)
Hypersensitivity	0 (0.0)	6 (2.04)
Urinary tract infection	11 (3.74)	8 (2.72)
Headache	11 (3.74)	12 (4.08)
Cough	5 (1.70)	10 (3.4)
Dyspnoea	6 (2.04)	6 (2.04)
Hypertension	5 (1.70)	17 (5.78)

A total of 52 serious adverse events were observed in 42 subjects during the trial of which, 29 events were observed in Desidustat group and 23 events observed in Darbepoetin group. In total, 12 (2.04%) subjects reported at least one TEAE leading to death: 6 (2.04%) in each of the treatment group. All the deaths are not related to study medication as per sponsor however 03 cases (02 in reference arm and 01 in test arm) have been evaluated to be related to the IP by regulatory authority. Subjects with at least one SAE is presented in table 4.

Table 4: SAEs reported in Desidustat and Darbepoetin alfa group up to week 24

Preferred term	Desidustat Oral Tablet (N = 294) n (%)	Darbepoetin Alfa Injection (N = 294) n (%)
Number of Subjects with at least one Serious Adverse Event	24 (8.16)	18 (6.12)
Immune thrombocytopenic purpura	1 (0.34)	0 (0.00)
Acute coronary syndrome	0 (0.00)	1 (0.34)
Acute myocardial infarction	0 (0.00)	1 (0.34)
Unstable angina	1 (0.34)	1 (0.34)
Wellen's syndrome	0 (0.00)	1 (0.34)
Hematemesis	0 (0.00)	1 (0.34)
Vomiting	0 (0.00)	1 (0.34)
Asthenia	1 (0.34)	0 (0.00)
Cardiac arrest	1 (0.34)	0 (0.00)
Death	2 (0.68)	2 (0.68)
Generalised oedema	0 (0.00)	1 (0.34)
COVID-19	1 (0.34)	0 (0.00)
Cellulitis	3 (1.02)	0 (0.00)
Dengue fever	1 (0.34)	0 (0.00)
Diabetic foot infection	1 (0.34)	1 (0.34)
Epididymitis	1 (0.34)	0 (0.00)
Intervertebral discitis	1 (0.34)	0 (0.00)
Lower respiratory tract infection	2 (0.68)	0 (0.00)
Pyelonephritis	0 (0.00)	1 (0.34)
Sepsis	0 (0.00)	1 (0.34)
Septic shock	1 (0.34)	0 (0.00)

Study: DESI.19.001 (DREAM-D)

A phase III, open label clinical trial comparing efficacy and safety of Desidustat oral tablet with Epoetin alfa injection on 392 patients with anaemia in chronic kidney disease dependent on dialysis reported a total of 373 adverse events during the trial. Total 185 subjects, 94 (47.96%) subjects in Desidustat group and 91 (46.43%) subjects in Epoetin alfa group, were reported with at least one TEAE during the trial. The most frequently reported TEAEs (reported in ≥ 2% of subjects in the either of the treatment groups) is presented in table 5.

Table 5: TEAEs reported in ≥ 2% of subjects in Desidustat and Epoetin alfa up to week 24

Preferred term	Desidustat Oral Tablet (N = 196) n (%)	Epoetin Alfa Injection (N = 196) n (%)
Number of Subjects with at least one TEAE	94 (47.96)	91 (46.43)
Nausea	7 (3.57)	3 (1.53)
Vomiting	8 (4.08)	7 (3.57)
Diarrhoea	4 (2.04)	5 (2.55)
Chills	5 (2.55)	1 (0.51)
Oedema	4 (2.04)	1 (0.51)
Asthenia	8 (4.08)	7 (3.57)
Pyrexia	16 (8.16)	10 (5.10)
COVID-19	9 (4.59)	6 (3.06)
Blood alkaline phosphatase increased	4 (2.04)	1 (0.51)
Blood potassium increased	12 (6.1)	5 (2.5)
Headache	7 (3.57)	9 (4.59)
Dyspnoea	5 (2.55)	9 (4.59)
Cough	3 (1.53)	4 (2.04)
Hypertension	5 (2.55)	5 (2.55)

A total of 38 serious adverse events were observed in 37 subjects during the trial, out of which, 16 events were observed in Desidustat group and 22 events observed in Epoetin group. In total, 11 (2.81%) subjects reported at least one TEAE leading to death: 4 (2.04%) in Desidustat group and 7 (3.57%) subjects were in Epoetin group. None of the serious adverse events are related to study medication. Subjects with at least one SAE is presented in table 6.

Table 6: SAEs reported in Desidustat and Epoetin alfa group up to week 24

Preferred term	Desidustat Oral Tablet (N = 196) n (%)	Epoetin Alfa Injection (N = 196) n (%)
Number of Subjects with at least one SAE	16 (8.16)	21 (10.71)
Atrial fibrillation	1 (0.51)	0 (0.00)
Left ventricular failure	1 (0.51)	0 (0.00)
Death	1 (0.51)	4 (2.04)
Pyrexia	0 (0.00)	1 (0.51)
Bacterial infection	1 (0.51)	0 (0.00)
Bronchitis	0 (0.00)	1 (0.51)
COVID-19	4 (2.04)	3 (1.53)
COVID-19 pneumonia	0 (0.00)	1 (0.51)
Catheter related infection	1 (0.51)	0 (0.00)
Gastroenteritis	0 (0.00)	1 (0.51)
Lower respiratory tract infection viral	1 (0.51)	0 (0.00)
Mucormycosis	0 (0.00)	1 (0.51)
Pneumonia	0 (0.00)	1 (0.51)
Pulmonary sepsis	1 (0.51)	0 (0.00)
Femur fracture	1 (0.51)	0 (0.00)
Hypercalcaemia	0 (0.00)	1 (0.51)
Brain injury	1 (0.51)	0 (0.00)
Hypertensive encephalopathy	0 (0.00)	1 (0.51)
Metabolic encephalopathy	0 (0.00)	1 (0.51)
Dyspnoea	0 (0.00)	1 (0.51)
Pulmonary oedema	1 (0.51)	1 (0.51)
Respiratory distress	1 (0.51)	0 (0.00)
Renal transplant	0 (0.00)	2 (1.02)
Accelerated hypertension	0 (0.00)	2 (1.02)
Jugular vein thrombosis	1 (0.51)	0 (0.00)
Venous thrombosis	0 (0.00)	1 (0.51)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

4.9 Overdose

No incidence of overdose with Desidustat has been reported. In case of overdose with Desidustat, general supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status.

5. Pharmacological properties

5.1 Mechanism of Action

Desidustat is an oral hypoxia-inducible factor prolyl hydroxylase domain (PHD) inhibitor (HIF-PHI) that stimulates erythropoiesis.

5.2 Pharmacodynamic Properties

Clinical development program of Desidustat has completed two phase 3 in study- one in "Anemia patient with CKD who are not on Dialysis (DREAM-ND)" and other phase 3 study in "Anemia patient with CKD who are on Dialysis (DREAM-D)".

Phase III Study (DREAM-ND)

Efficacy of Desidustat was studied in an open label, active controlled, non-inferiority phase III trial (DREAM ND) where 588 patients with stage 3-5 CKD, aged 18-80 years old and having haemoglobin level between 7-10 g/dL were randomized to receive either Desidustat oral tablet or Darbepoetin alfa injection for 24 weeks. Initial dose of Desidustat was 100 mg thrice a week. The dose of study drug was titrated to achieve either a hemoglobin of 10 to 12 g/dL or an absolute increase in hemoglobin of 2 g/dL over baseline. Primary efficacy end point was change in Hb levels from baseline to evaluation (Week 16 to Week 24) period in mITT population. A non-inferiority margin of -0.75 g/dL was selected to exclude a clinically relevant difference between the two treatment groups. The LS mean change from baseline to Hb (16–24) was 1.94 g/dl and 1.83 g/dl for Desidustat and Darbepoetin, respectively, with the estimated difference of 0.11 g/dl (95% CI, –0.1224 to 0.3464 g/dl) between the two groups; the lower limit of the 95% CI was above the predefined non inferiority margin of –0.75 g/dl, confirming the non-inferiority of Desidustat to Darbepoetin.

Table 7: Analysis of change from baseline in Hemoglobin (g/dL) in **mITT Population in DREAM ND** :

	Desidustat oral tablet (N=261)	Darbepoetin Alfa Injection (N=268)
Baseline Hb (Mean ± SD)	8.97±0.73	8.92±0.70
Average Hb of Week 16,20 and 24 (Mean ± SD)	10.90±1.36	10.77±1.46
Change from baseline (Mean ± SD)	1.93±1.37	1.84±1.46
LSM (SE)	1.9452 (0.0849)	1.8332 (0.0838)
Difference of LSM (SE)	0.1120 (0.1193)	
95% Confidence Interval	**-0.1224 ,0.3464 (p-value: 0.3483)**	
Lower margin of 95% CI of difference of LSM (SE) is less than -0.75 g/dL- **Non-inferiority achieved.**		

Phase III Study (DREAM-D)

In DREAM D, an open label trial of 392 patients of dialysis dependent CKD with hemoglobin levels between 8-11 g/dL, subjects were randomised to receive either Desidustat oral tablets or Epoetin injections for 24 weeks. Initial dose of Desidustat was 100-150 mg (Depending on subject's weight and prior use of erythropoietin analogue) orally three times a week. The dose of study drug was titrated to achieve hemoglobin of 10 to 12 g/dL. Estimation of efficacy was done by evaluation of difference of mean change of hemoglobin from baseline to evaluation period (week 16-24) between Desidustat group and Epoetin alfa group. The LS mean change from baseline to Hb (16–24) was 0.95 g/dl and 0.81 g/dl for Desidustat and Epoetin, respectively, with the estimated difference of 0.14 g/dl (95% CI, –0.1304 to 0.4202 g/dl) between the two groups; the lower limit of the 95% CI was above the predefined non inferiority margin of –1.0 g/dl, confirming the non-inferiority of Desidustat to Epoetin alfa.

Table 8: Analysis of change from baseline in Hemoglobin (gm/dL) in **mITT Population in DREAM D**:

	Desidustat oral tablet (N=184)	Epoetin Alfa Injection (N=189)
Baseline Hb (Mean ± SD)	9.57±0.98	9.46±1.14
Average Hb of Week 16,20 and 24 (Mean ± SD)	10.47±1.37	10.32±1.41
Change from baseline (Mean ± SD)	0.92±1.44	0.85±1.56
LSM (SE)	0.9545 (0.0996	0.8096 (0.0982)