Vipidia™

Generic name
Alogliptin

Composition
Each tablet contains 25 mg, 12.5 mg or 6.25mg as alogliptin.
Tablet core: Mannitol, Microcrystalline cellulose, Hydroxypropylcellulose, Croscarmellose sodium and Magnesium stearate

Tablet film coat: Hypromellose, Titanium dioxide (the above contained in all tablets), Yellow ferric oxide (containedin only 25 mg and 12.5 mg tablets), Red ferric oxide (contained in only 6.25 mg tablets)

Dosage form(s)
Film-coated tablet.

Indications
Therapeutic indications
Type 2 diabetes mellitus

Monotherapy
Adjunct therapy for dietary treatment and/or exercise therapy
Combination therapy (in addition to dietary treatment and/or exercise therapy)
Combination therapy with α-glucosidase inhibitors
Combination therapy with thiazolidinediones
Combination therapy with sulfonylurea
Combination therapy with biguanide.

Posology & method of administration
Posology
25 mg of alogliptin is orally administered once a day.
Summary of special remarks for the posology in special populations

Population	Japan
Elderly patients	N/A (Since the elderly often have reduced renal function, the dosage should be adjusted appropriately according to the degree of renal impairment.)
Pediatric patients	No data
Impaired renal	<mild> N/A

Population	Japan
function	<moderate to severe, including End Stage Renal Disease (ESRD)> Careful administration: Dosage should be reduced according to the degree of renal function, since blood concentrations of alogliptin may increase due to a delay in the excretion in patients with more severe than moderate renal impairment. **Moderate** renal impairment: 12.5 mg once daily **Severe** renal impairment (including ESRD): 6.25mg once daily
Impaired hepatic function	**N/A**

Method of Administration
For oral use.

Contra-indications
This product is contraindicated in patients with known hypersensitivity to alogliptin or any of its components.

Warnings and Precautions
For patients with moderate renal insufficiency (creatinine clearance ≥30 to <50 mL/min),one-half of the therapeutic dose of this drug should be administered.

For patients with severe renal insufficiency (creatinine clearance <30 mL/min), or withEnd-Stage Renal Disease (ESRD) requiring dialysis, one-quarter of the therapeutic dose of this drug should be administered.

Effects on ability to drive and use machines
The data do not suggest that alogliptin will affect the ability to drive or operate machinery or impair mental ability

Renal insufficiency
Alogliptin is primarily renally excreted. No dose-limiting toxicities were observed with single doses of alogliptin up to 800 mg in healthy subjects and multiple doses of 100 mg QD for 12 weeks or 400 mg QD for 14 days in subjects with T2DM. Since patients with diabetes may have compromised renal function, a renal impairment study was conducted to compare the pharmacokinetics of alogliptin in patients with various degrees of renal impairment to healthy age- and gender-matched controls. Exposure to alogliptin increased with severity of renal impairment. The mean AUC[0-tlqc] of alogliptin was 1.69-, 2.08-, 3.19- and 3.81-fold, higher in subjects with mild (creatinine clearance ≥50 to <80 mL/min), moderate (creatinine clearance ≥30 to <50 mL/min), or severe (creatinine clearance <30 mL/min) renal impairment

and with ESRD compared to healthy subjects, respectively. The distribution of exposure values for alogliptin in subjects with mild renal impairment was within the same range as that of healthy subjects with normal renal function; therefore no dose adjustment is recommended for patients with mild renal impairment. Dose reductions proportional to theseincreases in exposure are recommended for subjects with moderate and severe renal impairment/ESRD.

Drug interactions

No clinically meaningful interactions (with both drug and food) were observed, and no need for dose adjustment of alogliptin or other concomitantly administered drugs was identified.

Undesirable effects

Headache
- Pruritus
- Rash
- Abdominal pain
- Pharyngolaryngeal pain
- Peripheral edema
- Hypersensitivity

Overdose

No cases of alogliptin overdose were reported during clinical development, as of Dec. 2007.The highest doses of alogliptin administered in clinical trials were single doses of 800 mg to healthy subjects and multiple doses of 400 mg QD for 14 days to subjects with T2DM. No dose-limiting toxicities were observed at these dose levels. In the event of an overdose, it is reasonable to initiate removal of unabsorbed material from the gastrointestinal tract, and institute the necessary clinical monitoring and supportive therapy as dictated by the patient's clinical status.

Alogliptin is modestly dialyzable; after 3 hours of hemodialysis, approximately 7.24% of the drug was removed. Therefore, hemodialysis is unlikely to be beneficial in an overdose situation. It is not known if alogliptin is dialyzable by peritoneal dialysis.

Pharmacodynamics

Single-dose administration of Alogliptin to healthy subjects resulted in a peak inhibition of DPP-4 within 2 to 3 hours after dosing. The peak inhibition of DPP-4 exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses greater than or equal to 25 mg. Peak and total exposure over 24 hours to active GLP-1 were 3- to 4-fold greater with Alogliptin (at doses of 25 to 200 mg) than placebo. In a 16-week, double-blind, placebo-controlled study, Alogliptin 25 mg demonstrated decreases in postprandial glucagon while increasing postprandial active GLP-1 levels compared to placebo over an 8-hour period following a standardized meal. It is unclear how these findings relate to changes in overall glycemic control in patients with type 2 diabetes mellitus. In this study, Alogliptin 25 mg demonstrated decreases in 2-hour postprandial glucose compared to placebo

(-30 mg/dL versus 17 mg/dL, respectively). Multiple-dose administration of alogliptin to patients with type 2 diabetes also resulted in a peak inhibition of DPP-4 within 1 to 2 hours and exceeded 93% across all doses (25 mg, 100 mg, and 400 mg) after a single dose and after 14 days of once-daily dosing. At these doses of Alogliptin, inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing.

Pharmacokinetics
The pharmacokinetics of alogliptin has been studied in healthy subjects and in patients with type 2 diabetes. After administration of single, oral doses up to 800 mg in healthy subjects, the peak plasma alogliptin concentration (median Tmax) occurred 1 to 2 hoursafter dosing. At the maximum recommended clinical dose of 25 mg, alogliptin was eliminated with a mean terminal half-life (T1/2) of approximately 21 hours. After multiple-dose administration up to 400 mg for 14 days in patients with type 2diabetes, accumulation of alogliptin was minimal with an increase in total (i.e., AUC) and peak (i.e., Cmax) alogliptin exposures of 34% and 9%, respectively. Total and peak exposure to alogliptin increased proportionally across single doses and multiple dosesof alogliptin ranging from 25 mg to 400 mg. The inter-subject coefficient of variation for alogliptin AUC was 17%. The pharmacokinetics of alogliptin was also shown to be similar in healthy subjects and in patients with type 2 diabetes.

Absorption
The absolute bioavailability of alogliptin is approximately 100%. Administration of alogliptin with a high-fat meal results in no significant change in total and peak exposureto alogliptin. Alogliptin may therefore be administered with or without food.

Distribution
Following a single, 12.5 mg intravenous infusion of alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L, indicating that the drug is well distributed into tissues. Alogliptin is 20% bound to plasma proteins.

Metabolism
Alogliptin does not undergo extensive metabolism and 60% to 71% of the dose is excreted as unchanged drug in the urine. Two minor metabolites were detected following administration of an oral dose of [14C] alogliptin, *N*-demethylated, M-I (<1% of the parent compound), and *N*-acetylated alogliptin, M-II (<6% of the parent compound). M-I is an active metabolite and is an inhibitor of DPP-4 similar to the parent molecule; M-II does not display any inhibitory activity towards DPP-4 or other DPP-related enzymes. *In vitro* data indicate that CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

Alogliptin exists predominantly as the (*R*)-enantiomer (>99%) and undergoes little or no chiral conversion *in vivo* to the (*S*)-enantiomer. The (*S*)-enantiomer is not detectable at the 25 mg dose.

Excretion
The primary route of elimination of [14C] alogliptin-derived radioactivity occurs via renal excretion (76%) with 13% recovered in the feces, achieving a total recovery of 89% of the administered radioactive dose. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr.

Incompatibilities
Not Applicable

Shelf- life
36 Months

Packaging information / Nature and specification of the container
25 mg tablets and 12.5 mg tablets: packs of 100, 500 and 700 tablets
6.25 mg tablets: packs of 100, 140 and 500 tablets
Blister package: PCTFE, PP/Al
Bottle/Closure: HDPE/PP with PE filler

Storage and handling instructions
Store below 30°C.

Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)

Pregnancy
This drug should be used during pregnancy only if the benefits outweigh the risks to the mother and fetus. It is unknown if alogliptin is excreted into breast milk. Caution should be exercised when this drug is administered during lactation.

Breastfeeding
Caution should be exercised when this drug is administered during lactation.

Antidote for overdosing
Not applicable

List of excipients
Tablet core:
Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate

Table film coat:
Hypromellose,
Titanium dioxide
Yellow ferric oxide (contained in only 25 mg and 12.5 mg tablets), Red ferric oxide (contained in only 6.25 mg tablets)

Manufactured by
UBI, Taiwan,
Hsin-Chu Plant 1
No. 1 Kwang Fu Road, Hu – Ko
Hsin-Chu Hsien, Taiwan, Republic of China

Imported and Marketed by:
Takeda Pharmaceuticals India Pvt. Ltd.
701 - Executive Centre,
The Capital, Opposite ICICI bank,
Bandra Kurla Complex, Bandra East,
Mumbai 400 051, India