SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vipidia 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vipidia 25 mg film-coated tablets
Each tablet contains alogliptin benzoate equivalent to 25 mg alogliptin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Vipidia 25 mg film-coated tablets
Light red, oval (approximately 9.1 mm long by 5.1 mm wide), biconvex, film-coated tablets with "TAK" and "ALG-25" printed in grey ink on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vipidia is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

Posology

For the different dose regimens, Vipidia is available in strength of 25 mg film-coated tablets.

Adults (≥ 18 years old)
The recommended dose of alogliptin is one tablet of 25 mg once daily as add-on therapy to metformin, a thiazolidinedione, a sulphonylurea, or insulin or as triple therapy with metformin and a thiazolidinedione or insulin.

When alogliptin is used in combination with metformin and/or a thiazolidinedione, the dose of metformin and/or the thiazolidinedione should be maintained, and Vipidia administered concomitantly.

When alogliptin is used in combination with a sulphonylurea or insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see section 4.4).

Caution should be exercised when alogliptin is used in combination with metformin and a thiazolidinedione as an increased risk of hypoglycaemia has been observed with this triple therapy (see section 4.4). In case of hypoglycaemia, a lower dose of the thiazolidinedione or metformin may be considered.

Special populations
Elderly (≥ 65 years old)
No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function in this population.

Renal impairment
For patients with mild renal impairment (creatinine clearance (CrCl) > 50 to ≤ 80 mL/min), no dose adjustment of alogliptin is necessary (see section 5.2).

Alogliptin is not recommended for patients with moderate renal impairment (CrCl ≥ 30 to ≤ 50 mL/min), because these patients require a 12.5 mg dose which is not available (see section 5.2). The alogliptin tablets should not be split.

Alogliptin is not recommended for patients with severe renal impairment (CrCl < 30 mL/min) or end-stage renal disease requiring dialysis because these patients require a 6.25 mg dose which is not available. Experience in patients requiring renal dialysis is limited. Alogliptin has not been studied in patients undergoing peritoneal dialysis (see sections 4.4 and 5.2). The alogliptin tablets should not be split.

Appropriate assessment of renal function is recommended prior to initiation of treatment and periodically thereafter (see section 4.4).

Hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh scores of 5 to 9). Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9) and is, therefore, not recommended for use in such patients (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Vipidia in children and adolescents < 18 years old have not been established. No data are available.

Method of administration

Oral use.

Vipidia should be taken once daily with or without food. The tablets should be swallowed whole with water.

If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl-peptidase-4 (DPP-4) inhibitor (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

General

Vipidia should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Vipidia is not a substitute for insulin in insulin-requiring patients.

Use with other antihyperglycaemic medicinal products and hypoglycaemia

Due to the increased risk of hypoglycaemia in combination with a sulphonylurea, insulin or combination therapy with thiazolidinedione plus metformin, a lower dose of these medicinal products may be considered to reduce the risk of hypoglycaemia when these medicinal products are used in combination with alogliptin (see section 4.2).

Combinations not studied

Alogliptin has not been studied in combination with sodium glucose co-transporter 2 (SGLT-2) inhibitors or glucagon like peptide 1 (GLP-1) analogues nor formally as triple therapy with metformin and a sulphonylurea.

Renal impairment

As there is a need for dose adjustment in patients with moderate or severe renal impairment, or end-stage renal disease requiring dialysis, appropriate assessment of renal function is recommended prior to initiation of alogliptin therapy and periodically thereafter (see section 4.2).

Experience in patients requiring renal dialysis is limited. Alogliptin has not been studied in patients undergoing peritoneal dialysis (see sections 4.2 and 5.2).

Hepatic impairment

Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9) and is, therefore, not recommended for use in such patients (see sections 4.2 and 5.2).

Cardiac failure

Experience of alogliptin use in clinical studies in patients with congestive heart failure of New York Heart Association (NYHA) functional class III and IV is limited and caution is warranted in these patients.

Hypersensitivity reactions

Hypersensitivity reactions, including anaphylactic reactions, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome and erythema multiforme have been observed for DPP-4 inhibitors and have been spontaneously reported for alogliptin in the post-marketing setting. In clinical studies of alogliptin, anaphylactic reactions were reported with a low incidence.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. In a pooled analysis of the data from 13 studies, the overall rates of pancreatitis reports in patients treated with 25 mg alogliptin, 12.5 mg alogliptin, active control or placebo were 2, 1, 1 or 0 events per 1,000 patient years, respectively. In the cardiovascular outcomes study the rates of pancreatitis reports in patients treated with alogliptin or placebo were 3 or 2 events per 1,000 patient years, respectively. There have been spontaneously reported adverse reactions of acute pancreatitis in the post-marketing setting. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain, which may radiate to the back. If pancreatitis is suspected, Vipidia should be discontinued; if acute pancreatitis is confirmed, Vipidia should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hepatic effects

Postmarketing reports of hepatic dysfunction including hepatic failure have been received. A causal relationship has not been established. Patients should be observed closely for possible liver abnormalities. Obtain liver function tests promptly in patients with symptoms suggestive of liver

injury. If an abnormality is found and an alternative etiology is not established, consider discontinuation of alogliptin treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on alogliptin

Alogliptin is primarily excreted unchanged in the urine and metabolism by the cytochrome (CYP) P450 enzyme system is negligible (see section 5.2). Interactions with CYP inhibitors are thus not expected and have not been shown.

Results from clinical interaction studies also demonstrate that there are no clinically relevant effects of gemfibrozil (a CYP2C8/9 inhibitor), fluconazole (a CYP2C9 inhibitor), ketoconazole (a CYP3A4 inhibitor), cyclosporine (a p-glycoprotein inhibitor), voglibose (an alpha-glucosidase inhibitor), digoxin, metformin, cimetidine, pioglitazone or atorvastatin on the pharmacokinetics of alogliptin.

Effects of alogliptin on other medicinal products

In vitro studies suggest that alogliptin does not inhibit nor induce CYP 450 isoforms at concentrations achieved with the recommended dose of 25 mg alogliptin (see section 5.2). Interaction with substrates of CYP 450 isoforms are thus not expected and have not been shown. In studies *in vitro*, alogliptin was found to be neither a substrate nor an inhibitor of key transporters associated with disposition of the active substance in the kidney: organic anion transporter-1, organic anion transporter-3 or organic cationic transporter-2 (OCT2). Furthermore, clinical data do not suggest interaction with p-glycoprotein inhibitors or substrates.

In clinical studies, alogliptin had no clinically relevant effect on the pharmacokinetics of caffeine, (R)-warfarin, pioglitazone, glyburide, tolbutamide, (S)-warfarin, dextromethorphan, atorvastatin, midazolam, an oral contraceptive (norethindrone and ethinyl oestradiol), digoxin, fexofenadine, metformin, or cimetidine, thus providing *in vivo* evidence of a low propensity to cause interaction with substrates of CYP1A2, CYP3A4, CYP2D6, CYP2C9, p-glycoprotein, and OCT2.

In healthy subjects, alogliptin had no effect on prothrombin time or International Normalised Ratio (INR) when administered concomitantly with warfarin.

Combination with other anti-diabetic medicinal products

Results from studies with metformin, pioglitazone (thiazolidinedione), voglibose (alpha-glucosidase inhibitor) and glyburide (sulphonylurea) have shown no clinically relevant pharmacokinetic interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of alogliptin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of alogliptin during pregnancy.

Breast-feeding

It is unknown whether alogliptin is excreted in human milk. Animal studies have shown excretion of alogliptin in milk (see section 5.3). A risk to the suckling child cannot be excluded.

A decision on whether to discontinue breast-feeding or to discontinue alogliptin therapy should be made taking into account the benefit of breast-feeding for the child and the benefit of alogliptin therapy for the woman.

Fertility

The effect of alogliptin on fertility in humans has not been studied. No adverse effects on fertility were observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Vipidia has no or negligible influence on the ability to drive and use machines. However patients should be alerted to the risk of hypoglycaemia especially when combined with a sulphonylurea, insulin or combination therapy with thiazolidinedione plus metformin.

4.8 Undesirable effects

Summary of the safety profile

The information provided is based on a total of 9,405 patients with type 2 diabetes mellitus, including 3,750 patients treated with 25 mg alogliptin and 2,476 patients treated with 12.5 mg alogliptin, who participated in one phase 2 or 12 phase 3 double-blind, placebo- or active-controlled clinical studies. In addition, a cardiovascular outcomes study with 5,380 patients with type 2 diabetes mellitus and a recent acute coronary syndrome event was conducted with 2,701 randomised to alogliptin and 2,679 randomised to placebo. These studies evaluated the effects of alogliptin on glycaemic control and its safety as monotherapy, as initial combination therapy with metformin or a thiazolidinedione, and as add-on therapy to metformin, or a sulphonylurea, or a thiazolidinedione (with or without metformin or a sulphonylurea), or insulin (with or without metformin).

In a pooled analysis of the data from 13 studies, the overall incidences of adverse events, serious adverse events and adverse events resulting in discontinuation of therapy were comparable in patients treated with 25 mg alogliptin, 12.5 mg alogliptin, active control or placebo. The most common adverse reaction in patients treated with 25 mg alogliptin was headache.

The safety of alogliptin between the elderly (≥ 65 years old) and non-elderly (< 65 years old) was similar.

Tabulated list of adverse reactions

The adverse reactions are listed by system organ class and frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data).

In the pooled pivotal phase 3 controlled clinical studies of alogliptin as monotherapy and as add-on combination therapy involving 5,659 patients, the observed adverse reactions are listed below (Table 1).

Table 1: Adverse reactions

System organ class Adverse reaction	**Frequency of adverse reactions**
Infections and infestations	
upper respiratory tract infections	common
nasopharyngitis	common
Immune system disorders	
hypersensitivity	not known
Metabolism and nutrition disorders	
hypoglycaemia	common
Nervous system disorders	
headache	common
Gastrointestinal disorders	
abdominal pain	common
gastroesophageal reflux disease	common
diarrhoea	common
acute pancreatitis	not known
Hepatobiliary disorders	
hepatic dysfunction including hepatic failure	not known
Skin and subcutaneous tissue disorders	
pruritus	common
rash	common
exfoliative skin conditions including Stevens-Johnson syndrome	not known
erythema multiforme	not known
angioedema	not known
urticaria	not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

The highest doses of alogliptin administered in clinical studies were single doses of 800 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type 2 diabetes mellitus (equivalent to 32 times and 16 times the recommended daily dose of 25 mg alogliptin, respectively).

Management

In the event of an overdose, appropriate supportive measures should be employed as dictated by the patient's clinical status.

Minimal quantities of alogliptin are removed by haemodialysis (approximately 7% of the substance was removed during a 3-hour haemodialysis session). Therefore, haemodialysis is of little clinical benefit in overdose. It is not known if alogliptin is removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes; dipeptidyl peptidase 4 (DPP-4) inhibitors.

ATC code: A10BH04.

Mechanism of action and pharmacodynamic effects

Alogliptin is a potent and highly selective inhibitor of DPP-4, >10,000-fold more selective for DPP-4 than other related enzymes including DPP-8 and DPP-9. DPP-4 is the principal enzyme involved in the rapid degradation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and GIP (glucose-dependent insulinotropic polypeptide), which are released by the intestine and levels are increased in response to a meal. GLP-1 and GIP increases insulin biosynthesis and secretion from pancreatic beta cells, while GLP-1 also inhibits glucagon secretion and hepatic glucose production. Alogliptin therefore improves glycaemic control via a glucose-dependent mechanism, whereby insulin release is enhanced and glucagon levels are suppressed when glucose levels are high.

Clinical efficacy

Alogliptin has been studied as monotherapy, as initial combination therapy with metformin or a thiazolidinedione, and as add-on therapy to metformin, or a sulphonylurea, or a thiazolidinedione (with or without metformin or a sulphonylurea), or insulin (with or without metformin).

Administration of 25 mg alogliptin to patients with type 2 diabetes mellitus produced peak inhibition of DPP-4 within 1 to 2 hours and exceeded 93% both after a single 25 mg dose and after 14 days of once-daily dosing. Inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing. When the 4-hour postprandial glucose concentrations were averaged across breakfast, lunch and dinner, 14 days of treatment with 25 mg alogliptin resulted in a mean placebo-corrected reduction from baseline of -35.2 mg/dL.

Both 25 mg alogliptin alone and in combination with 30 mg pioglitazone demonstrated significant decreases in postprandial glucose and postprandial glucagon whilst significantly increasing postprandial active GLP-1 levels at Week 16 compared to placebo ($p<0.05$). In addition, 25 mg alogliptin alone and in combination with 30 mg pioglitazone produced statistically significant ($p<0.001$) reductions in total triglycerides at Week 16 as measured by postprandial incremental $AUC_{(0-8)}$ change from baseline compared to placebo.

A total of 14,779 patients with type 2 diabetes mellitus, including 6,448 patients treated with 25 mg alogliptin and 2,476 patients treated with 12.5 mg alogliptin, participated in one phase 2 or 13 phase 3 (including the cardiovascular outcomes study) double-blind, placebo- or active-controlled clinical studies conducted to evaluate the effects of alogliptin on glycaemic control and its safety. In these studies, 2,257 alogliptin-treated patients were ≥ 65 years old and 386 alogliptin-treated patients were ≥ 75 years old. The studies included 5,744 patients with mild renal impairment, 1,290 patients with moderate renal impairment and 82 patients with severe renal impairment / end-stage renal disease treated with alogliptin.

Overall, treatment with the recommended daily dose of 25 mg alogliptin improved glycaemic control when given as monotherapy and as initial or add-on combination therapy. This was determined by clinically relevant and statistically significant reductions in glycosylated haemoglobin (HbA1c) and fasting plasma glucose compared to control from baseline to study endpoint. Reductions in HbA1c were similar across different subgroups including renal impairment, age, gender and body mass index, while differences between races (e.g. White and non-White) were small. Clinically meaningful reductions in HbA1c compared to control were also observed with 25 mg alogliptin regardless of baseline background treatment. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Generally, the effects of alogliptin on body weight and lipids were neutral.

Alogliptin as monotherapy

Treatment with 25 mg alogliptin once daily resulted in statistically significant improvements from baseline in HbA1c and fasting plasma glucose compared to placebo-control at Week 26 (Table 2).

Alogliptin as add-on therapy to metformin
The addition of 25 mg alogliptin once daily to metformin hydrochloride therapy (mean dose = 1,847 mg) resulted in statistically significant improvements from baseline in HbA1c and fasting plasma glucose at Week 26 when compared to the addition of placebo (Table 2). Significantly more patients receiving 25 mg alogliptin (44.4%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (18.3%) at Week 26 ($p<0.001$).

The addition of 25 mg alogliptin once daily to metformin hydrochloride therapy (mean dose = 1,835 mg) resulted in improvements from baseline in HbA1c at Week 52 and Week 104. At Week 52, the HbA1c reduction by 25 mg alogliptin plus metformin (-0.76%, Table 3) was similar to that produced by glipizide (mean dose = 5.2 mg) plus metformin hydrochloride therapy (mean dose = 1,824 mg, -0.73%). At Week 104, the HbA1c reduction by 25 mg alogliptin plus metformin (-0.72%, Table 3) was greater than that produced by glipizide plus metformin (-0.59%). Mean change from baseline in fasting plasma glucose at Week 52 for 25 mg alogliptin and metformin was significantly greater than that for glipizide and metformin ($p<0.001$). By Week 104, mean change from baseline in fasting plasma glucose for 25 mg alogliptin and metformin was -3.2 mg/dL compared with 5.4 mg/dL for glipizide and metformin. More patients receiving 25 mg alogliptin and metformin (48.5%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving glipizide and metformin (42.8%) ($p=0.004$).

Alogliptin as add-on therapy to a sulphonylurea
The addition of 25 mg alogliptin once daily to glyburide therapy (mean dose = 12.2 mg) resulted in statistically significant improvements from baseline in HbA1c at Week 26 when compared to the addition of placebo (Table 2). Mean change from baseline in fasting plasma glucose at Week 26 for 25 mg alogliptin showed a reduction of 8.4 mg/dL compared to an increase of 2.2 mg/dL with placebo. Significantly more patients receiving 25 mg alogliptin (34.8%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (18.2%) at Week 26 ($p=0.002$).

Alogliptin as add-on therapy to a thiazolidinedione
The addition of 25 mg alogliptin once daily to pioglitazone therapy (mean dose = 35.0 mg, with or without metformin or a sulphonylurea) resulted in statistically significant improvements from baseline in HbA1c and fasting plasma glucose at Week 26 when compared to the addition of placebo (Table 2). Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin or sulphonylurea therapy. Significantly more patients receiving 25 mg alogliptin (49.2%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (34.0%) at Week 26 ($p=0.004$).

Alogliptin as add-on therapy to a thiazolidinedione with metformin
The addition of 25 mg alogliptin once daily to 30 mg pioglitazone and metformin hydrochloride therapy (mean dose = 1,867.9 mg) resulted in improvements from baseline in HbA1c at Week 52 that were both non-inferior and statistically superior to those produced by 45 mg pioglitazone and metformin hydrochloride therapy (mean dose = 1,847.6 mg, Table 3). The significant reductions in HbA1c observed with 25 mg alogliptin plus 30 mg pioglitazone and metformin were consistent over the entire 52-week treatment period compared to 45 mg pioglitazone and metformin ($p<0.001$ at all time points). In addition, mean change from baseline in fasting plasma glucose at Week 52 for 25 mg alogliptin plus 30 mg pioglitazone and metformin was significantly greater than that for 45 mg pioglitazone and metformin ($p<0.001$). Significantly more patients receiving 25 mg alogliptin plus 30 mg pioglitazone and metformin (33.2%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving 45 mg pioglitazone and metformin (21.3%) at Week 52 ($p<0.001$).

Alogliptin as add-on therapy to insulin (with or without metformin)

The addition of 25 mg alogliptin once daily to insulin therapy (mean dose = 56.5 IU, with or without metformin) resulted in statistically significant improvements from baseline in HbA1c and fasting plasma glucose at Week 26 when compared to the addition of placebo (Table 2). Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin therapy. More patients receiving 25 mg alogliptin (7.8%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (0.8%) at Week 26.

Table 2: Change in HbA1c (%) from baseline with alogliptin 25 mg at Week 26 by placebo-controlled study (FAS, LOCF)

Study	**Mean baseline HbA1c (%) (SD)**	**Mean change from baseline in HbA1c (%)† (SE)**	**Placebo-corrected change from baseline in HbA1c (%)† (2-sided 95% CI)**
Monotherapy placebo-controlled study			
Alogliptin 25 mg once daily (n=128)	7.91 (0.788)	-0.59 (0.066)	-0.57* (-0.80, -0.35)
Add-on combination therapy placebo-controlled studies			
Alogliptin 25 mg once daily with metformin (n=203)	7.93 (0.799)	-0.59 (0.054)	-0.48* (-0.67, -0.30)
Alogliptin 25 mg once daily with a sulphonylurea (n=197)	8.09 (0.898)	-0.52 (0.058)	-0.53* (-0.73, -0.33)
Alogliptin 25 mg once daily with a thiazolidinedione ± metformin or a sulphonylurea (n=195)	8.01 (0.837)	-0.80 (0.056)	-0.61* (-0.80, -0.41)
Alogliptin 25 mg once daily with insulin ± metformin (n=126)	9.27 (1.127)	-0.71 (0.078)	-0.59* (-0.80, -0.37)

FAS = full analysis set
LOCF = last observation carried forward
† Least squares means adjusted for prior antihyperglycaemic therapy status and baseline values
* $p<0.001$ compared to placebo or placebo+combination treatment

Table 3: Change in HbA1c (%) from baseline with alogliptin 25 mg by active-controlled study (PPS, LOCF)			
Study	**Mean baseline HbA1c (%) (SD)**	**Mean change from baseline in HbA1c (%)† (SE)**	**Treatment-corrected change from baseline in HbA1c (%)† (1-sided CI)**
Add-on combination therapy studies			
Alogliptin 25 mg once daily with metformin vs a sulphonylurea + metformin			
Change at Week 52 (n=382)	7.61 (0.526)	-0.76 (0.027)	-0.03 (-infinity, 0.059)
Change at Week 104 (n=382)	7.61 (0.526)	-0.72 (0.037)	-0.13* (-infinity, -0.006)
Alogliptin 25 mg once daily with a thiazolidinedione + metformin vs a titrating thiazolidinedione + metformin			
Change at Week 26 (n=303)	8.25 (0.820)	-0.89 (0.042)	-0.47* (-infinity, -0.35)
Change at Week 52 (n=303)	8.25 (0.820)	-0.70 (0.048)	-0.42* (-infinity, -0.28)

PPS = per protocol set
LOCF = last observation carried forward
* Non inferiority and superiority statistically demonstrated
† Least squares means adjusted for prior antihyperglycaemic therapy status and baseline values

Patients with renal impairment
The efficacy and safety of the recommended doses of alogliptin were investigated separately in a subgroup of patients with type 2 diabetes mellitus and severe renal impairment/end-stage renal disease in a placebo-controlled study (59 patients on alogliptin and 56 patients on placebo for 6 months) and found to be consistent with the profile obtained in patients with normal renal function.

Elderly (≥ 65 years old)
The efficacy of alogliptin in patients with type 2 diabetes mellitus and ≥ 65 years old across a pooled analysis of five 26-week placebo-controlled studies was consistent with that in patients < 65 years old.

In addition, treatment with 25 mg alogliptin once daily resulted in improvements from baseline in HbA1c at Week 52 that were similar to those produced by glipizide (mean dose = 5.4 mg). Importantly, despite alogliptin and glipizide having similar HbA1c and fasting plasma glucose changes from baseline, episodes of hypoglycaemia were notably less frequent in patients receiving 25 mg alogliptin (5.4%) compared to those receiving glipizide (26.0%).

Clinical safety

Cardiovascular Safety
In a pooled analysis of the data from 13 studies, the overall incidences of cardiovascular death, non fatal myocardial infarction and non-fatal stroke were comparable in patients treated with 25 mg alogliptin, active control or placebo.

In addition, a prospective randomised cardiovascular outcomes safety study was conducted with 5,380 patients with high underlying cardiovascular risk to examine the effect of alogliptin compared with placebo (when added to standard of care) on major adverse cardiovascular events (MACE) including time to the first occurrence of any event in the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke in patients with a recent (15 to 90 days) acute coronary event. At baseline, patients had a mean age of 61 years, mean duration of diabetes of 9.2 years, and mean HbA1c of 8.0%.

The study demonstrated that alogliptin did not increase the risk of having a MACE compared to placebo [Hazard Ratio: 0.96; 1-sided 99% Confidence Interval: 0-1.16]. In the alogliptin group, 11.3% of patients experienced a MACE compared to 11.8% of patients in the placebo group.

Table 4. MACE Reported in cardiovascular outcomes study

	Number of Patients (%)	
	Alogliptin 25 mg	**Placebo**
	N=2,701	N=2,679
Primary Composite Endpoint [First Event of CV Death, Nonfatal MI and Nonfatal Stroke]	**305 (11.3)**	**316 (11.8)**
Cardiovascular Death*	89 (3.3)	111 (4.1)
Nonfatal Myocardial Infarction	187 (6.9)	173 (6.5)
Nonfatal Stroke	29 (1.1)	32 (1.2)

*Overall there were 153 subjects (5.7%) in the alogliptin group and 173 subjects (6.5%) in the placebo group who died (all-cause mortality).

There were 703 patients who experienced an event within the secondary MACE composite endpoint (first event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and urgent revascularization due to unstable angina). In the alogliptin group, 12.7% (344 subjects) experienced an event within the secondary MACE composite endpoint, compared with 13.4% (359 subjects) in the placebo group [Hazard Ratio = 0.95; 1-sided 99% Confidence Interval: 0-1.14].

Hypoglycaemia
In a pooled analysis of the data from 12 studies, the overall incidence of any episode of hypoglycaemia was lower in patients treated with 25 mg alogliptin than in patients treated with 12.5 mg alogliptin, active control or placebo (3.6%, 4.6%, 12.9% and 6.2%, respectively). The majority of these episodes were mild to moderate in intensity. The overall incidence of episodes of severe hypoglycaemia was comparable in patients treated with 25 mg alogliptin or 12.5 mg alogliptin, and lower than the incidence in patients treated with active control or placebo (0.1%, 0.1%, 0.4% and 0.4%, respectively). In the prospective randomised controlled cardiovascular outcomes study, investigator reported events of hypoglycemia were similar in patients receiving placebo (6.5%) and patients receiving alogliptin (6.7%) in addition to standard of care.

In a clinical study of alogliptin as mono-therapy, the incidence of hypoglycaemia was similar to that of placebo, and lower than placebo in another study as add-on to a sulphonylurea.

Higher rates of hypoglycaemia were observed with triple therapy with thiazolidinedione and metformin and in combination with insulin, as observed with other DPP-4 inhibitors.

Patients (≥ 65 years old) with type 2 diabetes mellitus are considered more susceptible to episodes of hypoglycaemia than patients < 65 years old. In a pooled analysis of the data from 12 studies, the overall incidence of any episode of hypoglycaemia was similar in patients ≥ 65 years old treated with 25 mg alogliptin (3.8%) to that in patients < 65 years old (3.6%).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Vipidia in one or more subsets of the paediatric population in the treatment of type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of alogliptin has been shown to be similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption

The absolute bioavailability of alogliptin is approximately 100%.

Administration with a high-fat meal resulted in no change in total and peak exposure to alogliptin. Vipidia may, therefore, be administered with or without food.

After administration of single, oral doses of up to 800 mg in healthy subjects, alogliptin was rapidly absorbed with peak plasma concentrations occurring 1 to 2 hours (median T_{max}) after dosing.

No clinically relevant accumulation after multiple dosing was observed in either healthy subjects or in patients with type 2 diabetes mellitus.

Total and peak exposure to alogliptin increased proportionately across single doses of 6.25 mg up to 100 mg alogliptin (covering the therapeutic dose range). The inter-subject coefficient of variation for alogliptin AUC was small (17%).

Distribution

Following a single intravenous dose of 12.5 mg alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L indicating that the active substance is well distributed into tissues.

Alogliptin is 20-30% bound to plasma proteins.

Biotransformation

Alogliptin does not undergo extensive metabolism, 60-70% of the dose is excreted as unchanged active substance in the urine.

Two minor metabolites were detected following administration of an oral dose of [^{14}C] alogliptin, N-demethylated alogliptin, 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 a highly selective inhibitor of DPP-4 similar to alogliptin; 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.

In vitro studies indicate that alogliptin does not induce CYP1A2, CYP2B6 and CYP2C9 and does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at concentrations achieved with the recommended dose of 25 mg alogliptin. Studies *in vitro* have shown alogliptin to be a mild inducer of CYP3A4, but alogliptin has not been shown to induce CYP3A4 in studies *in vivo*.

In studies *in vitro*, alogliptin was not an inhibitor of the following renal transporters; OAT1, OAT3 and OCT2.

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 therapeutic doses.

Elimination

Alogliptin was eliminated with a mean terminal half-life ($T_{1/2}$) of approximately 21 hours.

Following administration of an oral dose of [^{14}C] alogliptin, 76% of total radioactivity was eliminated in the urine and 13% was recovered in the faeces.

The average renal clearance of alogliptin (170 mL/min) was greater than the average estimated glomerular filtration rate (approx. 120 mL/min), suggesting some active renal excretion.

Time-dependency

Total exposure ($AUC_{(0\text{-}inf)}$) to alogliptin following administration of a single dose was similar to exposure during one dose interval ($AUC_{(0\text{-}24)}$) after 6 days of once daily dosing. This indicates no time-dependency in the kinetics of alogliptin after multiple dosing.

Special populations

Renal impairment
A single-dose of 50 mg alogliptin was administered to 4 groups of patients with varying degrees of renal impairment (CrCl using the Cockcroft-Gault formula): mild (CrCl = > 50 to ≤ 80 mL/min), moderate (CrCl = ≥ 30 to ≤ 50 mL/min), severe (CrCl = < 30 mL/min) and end-stage renal disease on haemodialysis.

An approximate 1.7-fold increase in AUC for alogliptin was observed in patients with mild renal impairment. However, as the distribution of AUC values for alogliptin in these patients was within the same range as control subjects, no dose adjustment for patients with mild renal impairment is necessary (see section 4.2).

In patients with moderate or severe renal impairment, or end-stage renal disease on haemodialysis, an increase in systemic exposure to alogliptin of approximately 2- and 4-fold was observed, respectively. (Patients with end-stage renal disease underwent haemodialysis immediately after alogliptin dosing. Based on mean dialysate concentrations, approximately 7% of the active substance was removed during a 3-hour haemodialysis session.) Therefore, in order to maintain systemic exposures to alogliptin that are similar to those observed in patients with normal renal function, lower doses of alogliptin should be used in patients with moderate or severe renal impairment, or end-stage renal disease requiring dialysis (see section 4.2).

Hepatic impairment
Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment compared to healthy control subjects. The magnitude of these reductions was not considered to be clinically relevant. Therefore, no dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh scores of 5 to 9). Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9, see section 4.2).

Age, gender, race, body weight
Age (65-81 years old), gender, race (white, black and Asian) and body weight did not have any clinically relevant effect on the pharmacokinetics of alogliptin. No dose adjustment is necessary (see section 4.2).

Paediatric population
The pharmacokinetics of alogliptin in children and adolescents < 18 years old has not been established. No data are available (see section 4.2).

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and toxicology.

The no-observed-adverse-effect level (NOAEL) in the repeated dose toxicity studies in rats and dogs up to 26 and 39 weeks in duration, respectively, produced exposure margins that were approximately 147- and 227-fold, respectively, the exposure in humans at the recommended dose of 25 mg alogliptin.

Alogliptin was not genotoxic in a standard battery of *in vitro* and *in vivo* genotoxicity studies.

Alogliptin was not carcinogenic in 2-year carcinogenicity studies conducted in rats and mice. Minimal to mild simple transitional cell hyperplasia was seen in the urinary bladder of male rats at the lowest dose used (27 times the human exposure) without establishment of a clear NOEL (no observed effect level).

No adverse effects of alogliptin were observed upon fertility, reproductive performance, or early embryonic development in rats up to a systemic exposure far above the human exposure at the recommended dose. Although fertility was not affected, a slight, statistical increase in the number of abnormal sperm was observed in males at an exposure far above the human exposure at the recommended dose.

Placental transfer of alogliptin occurs in rats.

Alogliptin was not teratogenic in rats or rabbits with a systemic exposure at the NOAELs far above the human exposure at the recommended dose. Higher doses of alogliptin were not teratogenic but resulted in maternal toxicity, and were associated with delayed and/or lack of ossification of bones and decreased foetal body weights.

In a pre- and postnatal development study in rats, exposures far above the human exposure at the recommended dose did not harm the developing embryo or affect offspring growth and development. Higher doses of alogliptin decreased offspring body weight and exerted some developmental effects considered secondary to the low body weight.

Studies in lactating rats indicate that alogliptin is excreted in milk.

No alogliptin-related effects were observed in juvenile rats following repeat-dose administration for 4 and 8 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Microcrystalline cellulose

Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate

Film-coating

Hypromellose
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol 8000

Printing ink

Shellac
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

.
Store at temperature not exceeding 30°C

6.5 Nature and contents of container

Polychlorotrifluoroethylene (PCTFE)/polyvinyl chloride (PVC) blisters with push through aluminium, 28, film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals U.S.A Inc
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