Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Alogliptin (as benzoate)

Proprietary Product Name: Nesina, Vipidia

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

January 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New Chemical Entity
Decision:	Approved
Date of Decision:	10 September 2013
Active ingredient:	Alogliptin (as benzoate)
Product Names:	Nesina, Vipidia
Sponsor's Name and Address:	Takeda Pharmaceuticals Australia Pty Ltd Ground floor, 2-4 Lyonpark Road Macquarie Park NSW 2113
Dose form:	Film-coated tablet
Strengths:	6.25 mg, 12.5 mg and 25 mg
Container:	Blister pack
Pack sizes:	7, 10, 14, 28, 30, 56, 60, 90, 98 and 100
Approved Therapeutic use:	Nesina/Vipidia is indicated to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, insulin (with or without metformin), or in combination with metformin and a thiazolidinedione when dual therapy does not provide adequate glycaemic control.
Route of administration:	Oral
Dosage (abbreviated):	The recommended dose is 25 mg once daily. Vipidia/Nesina is not indicated for initial combination therapy. For patients with moderate renal impairment the recommended dose is 12.5 mg once daily. For patients with severe renal impairment or End-Stage Renal Disease (ESRD) requiring dialysis, the recommended dose is 6.25 mg once daily.
ARTG Numbers:	199538, 199539, 199540, 199541, 199542, 199543

Product background

Type 2 diabetes mellitus (T2DM) is a chronic condition resulting from three distinct deficiencies: impaired insulin secretion, insulin resistance and hypersecretion of glucagon.

T2DM is associated with a number of long-term microvascular and macrovascular complications (Campbell, 2000[1]).

Alogliptin is an oral anti-hyperglycaemic (anti-diabetic) agent that inhibits the activity of dipeptidyl peptidase-4 (DPP-4), which is an enzyme that degrades incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP).

This AusPAR describes the application by Takeda Pharmaceuticals Australia Pty Ltd (the sponsor) to register Nesina and Vipidia tablets containing 6.25 mg, 12.5 mg and 25 mg alogliptin (as benzoate) for the following proposed indications:

Add-on combination:

Nesina / Vipidia is indicated to improve glycaemic control in adult patients (≥18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, metformin and a thiazolidinedione, or insulin (with or without metformin).

Initial combination:

Nesina / Vipidia is indicated for use as initial combination with metformin to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control and dual alogliptin and metformin therapy is appropriate.

The proposed dose of alogliptin for the treatment of T2DM is one 25 mg tablet taken daily. Lower daily dose presentations are to be made available for patients with moderate renal impairment (12.5 mg) or end-stage renal disease (6.25 mg).

Regulatory status

Nesina and Vipidia tablets received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 September 2013.

At the time this application was considered by the TGA a similar application had been approved in Japan (April 2010) and the USA (January 2013) and was under consideration in the European Union (EU), Canada and Switzerland.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

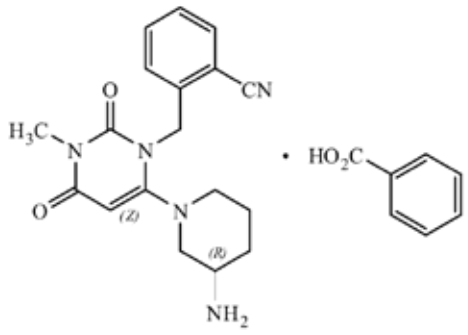
II. Quality findings

Drug substance (active ingredient)

Alogliptin is related to a number of other DPP-4 inhibitors (saxagliptin, sitagliptin, vildagliptin and linagliptin), which have a similar pharmacological action. The structure of alogliptin benzoate is shown in Figure 1.

[1] Campbell IW. Epidemiology and clinical presentation of type 2 diabetes. *Value Health* 2000;3(Suppl 1):S-3-6.

Figure 1. Structure of alogliptin benzoate



Alogliptin benzoate is a white to off-white, non-hygroscopic, crystalline powder. Two crystalline forms of the drug substance are known. At 25°C, alogliptin benzoate is sparingly soluble in water (2-3%) over the pH range 3-11. It contains one chiral centre and is produced as the *R*-enantiomer.

Alogliptin has a pKa of 8.5. The octanol/water partition coefficient (log P) is about 0.6. Alogliptin is considered Biopharmaceutics Classification System (BCS) Class I (high solubility, high permeability).

The particle size of the drug substance is controlled.

Drug product

The drug products proposed for registration are immediate-release, unscored, film-coated tablets for oral administration, containing 8.5 mg, 17 mg, and 34 mg of alogliptin benzoate, equivalent to 6.25 mg, 12.5 mg, and 25 mg alogliptin. Blister packs containing 7, 10, 14, 28, 30, 56, 60, 90, 98 and 100 tablets are proposed for registration, although not all pack sizes may be marketed in Australia.

The tablets are film-coated tablets. As the drug is highly soluble over the entire physiological pH range, the dissolution rate of the tablets is rapid.

The 12.5 mg and 25 mg tablets show excellent stability, and the proposed shelf life of 4 years below 25°C is acceptable. For the 6.25 mg tablets the shelf life has been restricted to 3 years below 25°C.

Biopharmaceutics

The tablets proposed for registration have been shown to be bioequivalent to the tablets used in Phase III clinical studies, and food has been shown to have no significant effect on their rate and extent of absorption. The absolute bioavailability of the tablets is about 100%.

Advisory committee considerations

The submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 150th meeting in March 2013. The PSC advice included the following:

1. The PSC endorsed all the issues raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects of the submission. In addition, the PSC advised that the sponsor should be asked to ensure that drug substance manufactured at all nominated manufacturing sites are included in the drug product stability trial protocols.

2. With regards to the population PK analysis, the PSC:
   - Advised that the data in relation to clearance (CL) versus creatinine clearance were not consistent.
   - Raised concerns about p-glycoprotein interactions in relation to more sensitive drugs.
   - Advised that the absence of data on half maximal effective concentration (EC50) makes it hard to predict concentration over a 24 h period.

There was no requirement for this submission to be reviewed again by the PSC before it was presented for consideration by the ACPM.

Quality summary and conclusions

All issues raised concerning chemistry and quality control aspects have been satisfactorily resolved. The PSC comments concerning population PK data have been referred to the clinical Delegate.

There are no objections in respect of chemistry, manufacturing and controls to registration of the proposed products.

III. Nonclinical findings

Introduction

General comments

The overall quality of the non-clinical dossier was good with all pivotal safety studies conducted according to good laboratory principles (GLP).

Pharmacology

Primary pharmacology

The incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) stimulate glucose-dependent insulin secretion by beta cells (b-cells) in the pancreas and stimulate the proliferation of these b-cells in the pancreas. GLP-1 additionally stimulates insulin biosynthesis by pancreatic b-cells, inhibits glucagon secretion from pancreatic α-cells and inhibits gastric emptying. Dipeptidyl peptidase-4 (DPP-4) is an enzyme which catalyses the removal of the N-terminal dipeptide from these hormones and thus inactivates them. Alogliptin is an inhibitor of DPP-4 and it is anticipated that it will enhance the active levels of GLP-1 and GIP and thus improve glycaemic control in patients with type 2 diabetes in situations where other interventions are not achieving this goal.

In vitro studies were directed towards establishing the inhibition profile of alogliptin (and metabolites) against DPP-4. The submitted studies established that alogliptin is an inhibitor of DPP-4 with concentrations causing 50% inhibition (IC_{50}) around 7 nM for this enzyme regardless of its source (recombinant human, dog plasma, rat plasma, human colonic adenocarcinoma (Caco-2) cells). The anticipated clinical minimum concentration

(C_{min}) is around 46 nM.[2] Therefore, the *in vitro* studies support the proposed clinical dose. Alogliptin was slightly more potent than either sitagliptin (registered as Januvia) or vildagliptin (registered as Galvus) against DPP-4 (IC_{50} values 6.9, 12.1 and 23.8 nM, respectively).

In vivo studies evaluated the effect of alogliptin on DPP-4 activity in normal (euglycaemic) animals and in various animal models of T2DM. Oral administration of alogliptin to normoglycaemic rats, dogs, and monkeys effectively inhibited plasma DPP-4 activity. Toxicokinetics were performed in the monkey mechanistic study and 90% inhibition over the first 3 h was achieved at 1.7 mg/kg single oral dose which achieved an exposure 1.3 times the anticipated clinical $AUC_{0\text{-}24h}$. At this dose, 81–84% inhibition was still evident at 24 h post-dose.

Efficacy of alogliptin was assessed either by surrogate measures (DPP-4 inhibition in plasma samples, increased intact plasma GLP-1 levels) or by effects on diabetic parameters (glucose tolerance, insulin levels, glucose levels, glycosylated haemoglobin (GHb) levels and pancreatic morphology) in animals. A dose-dependent improvement in glucose tolerance, increased plasma levels of GLP-1 and insulin, decreased glycosylated haemoglobin, and increased pancreatic insulin content were consistently seen in diabetic mice and rats (*fa/fa*, rodent model of T2DM; N-STZ-1.5, rodent model for nonobese T2DM with impaired insulin secretion) that received alogliptin. Alogliptin had no effect on plasma glucose levels in normoglycaemic rats and monkeys.

The minimal effective dose in improving glucose tolerance and increasing plasma insulin was a single oral (PO) dose of 0.3 mg/kg in diabetic rats, while the minimal effective dose in decreasing glycosylated haemoglobin and increasing pancreatic insulin content in diabetic rats was 3 mg/kg/day PO for 4 weeks. The estimated AUC at these doses is below that expected clinically.

The pharmacology studies support the proposed clinical dose (25 mg) and the proposed dosing regimen (once daily). The studies also support the use of rats, dogs and monkeys in toxicity studies. It should be noted, however, that reduced DPP-4 inhibition was evident in fatty rats after 8 weeks of dosing compared with a single dose.

The metabolite M-I (desmethyl alogliptin) was equipotent with alogliptin against DPP-4 and also showed no activity against other members of the DPP-4 activity and/or structure homologue (DASH) family. Metabolite M-II (N-acetyl alogliptin) showed no activity against DPP-4 or any other DASH family members. Alogliptin contains a single chiral centre and is proposed to be marketed as the *R*-isomer. The *S*-isomer of alogliptin showed some activity against DPP-4 (IC_{50} 1059 nM) but no activity against other members of the DASH family tested. Alogliptin is not extensively metabolised and both M-I and M-II accounted for less than 5% of the clinical exposure in terms of $AUC_{0\text{-}24h}$. The chiral conversion *in vivo* of the *R*-enantiomer of alogliptin to (*S*)-alogliptin was shown to be negligible. Therefore, M-I, M-II and (*S*)-alogliptin are not expected to contribute to the pharmacological activity.

Pharmacodynamic drug interactions

Interactions of alogliptin with other anti-diabetic agents were also examined in animal models of diabetes. Three studies examined the effects of alogliptin and pioglitazone alone and in combination, on diabetic indices in *db/db* mice. The single agents had the expected effects on the indices and had additive effects in decreasing GHb, triglycerides, non-esterified fatty acid (NEFA) levels, and glucose $AUC_{0\text{-}120\ min}$ and increasing the insulinogenic index. The effect of the two drugs combined was greater than additive in increasing pancreatic insulin content and the insulinogenic index and decreasing plasma glucose. Pioglitazone alone increases adiponectin levels in *db/db* mice. Alogliptin alone did not affect adiponectin levels and did not modify the effect of pioglitazone on adiponectin.

[2] Based on a C_{min} of 22.4 ng/mL (66 nM) and around 30% protein binding

Neither alogliptin nor pioglitazone alone had any effect on pancreatic islet morphology but the two drugs together restored insulin immunoreactivity and normal peripheral distribution of α-cells in the periphery of the islets.

Combination treatment with alogliptin and metformin to Wistar fatty rats additively decreased plasma glucose, synergistically increased plasma active GLP-1 levels and enhanced insulin secretion. In Wistar fatty rats pre-treated with pioglitazone, alogliptin or metformin alone decreased the plasma glucose $AUC_{0\text{-}120min}$ by 37% and 38%, respectively. Triple combination treatment with alogliptin/metformin/pioglitazone in these animals decreased the plasma glucose $AUC_{0\text{-}120min}$ by up to 55%.

Combination treatment with alogliptin and glibenclamide to N-STZ-1.5 rats additively decreased plasma glucose levels and additively increased plasma insulin levels. Combination of alogliptin and voglibose in the *db/db* mouse model produced synergistic effects in increasing pancreatic insulin and plasma intact GLP-1 levels and additive effects on other diabetic indices. Combination treatment with alogliptin and voglibose effectively preserved islet architecture and islet cell composition in *db/db* mice.

Overall, the pharmacodynamic (PD) drug interaction studies support the proposed combined use of alogliptin/metformin, alogliptin/pioglitazone (a thiazolidinedione), alogliptin/metformin/pioglitazone and alogliptin/glibenclamide (a sulfonylurea) in improving glycaemic control. No studies were submitted to support the use of alogliptin with insulin.

Secondary pharmacodynamics

In vitro, alogliptin had no detectable inhibitory activity on other members of the S9 peptidase or DASH family of serine proteases (human DPP-2, DPP-8, DPP-9, PREP or FAP) or on human tryptase (IC_{50} >100 μM; 200 times the clinical maximum concentration (C_{max})). The selectivity of alogliptin for DPP-4 over DPP-8 and DPP-9 was of the same order as linagliptin (>10000-fold) (refer to the Linagliptin AusPAR), and significantly greater than that for sitagliptin (>2700; Sitagliptin European Public Assessment Report (EPAR)), or vildagliptin or saxagliptin (which are 250–400-fold selective for DPP-4 over DPP-8 and 30–75-fold selective with respect to DPP-9; Vildagliptin AusPAR; Saxagliptin EPAR).

Radioligand binding assays and enzyme assays were used to examine potential off-target effects of alogliptin. The only significant activity of alogliptin (10 μM) was inhibition (50-65%) of naloxone binding to non-selective opioid receptors in the rat cerebral cortex. However, no significant inhibition of naloxone binding to selective human delta (δ), kappa (κ), and μ opioid receptor subtypes expressed in Chinese hamster ovary (CHO), human embryonic kidney-293 (HEK-293), and CHO-K1 cells, respectively, was observed. Given the extent of inhibition at 20 times the clinical C_{max} to opioid receptors in the rat cerebral cortex and the absence of inhibition on recombinantly expressed human receptors, this finding is not expected to be clinically-relevant.

In vivo secondary PD studies in Wistar fatty rats found no effect of 8 weeks dosing with alogliptin (up to 10 mg/kg/day PO) on weight gain or metabolic indices. Alogliptin (1 mg/kg) also had no effect on intestinal xylose absorption in Wistar fatty rats suggesting that the improved glucose tolerance seen in this animal model was not the result of inhibition of intestinal glucose absorption.

Safety pharmacology

In rats, alogliptin (up to 300 mg/kg for 28 days, approximately 70 times the anticipated clinical C_{max}) had no effects on central nervous system (CNS) function monitored with functional observation. There were no reports of any CNS effects in the repeat-dose toxicity or carcinogenicity studies in any species at high relative exposures.

Alogliptin caused slight inhibition (10%) of human ether-a-go-go related gene (hERG) channel currents at 30 μM (60 times the clinical C_{max}) *in vitro* and slight shortening (< 9%) of cardiac action potential duration in isolated dog Purkinje fibres (≤ 30 μM). No effects on any cardiac parameter (including QT_c[3]) were seen in dogs following single doses up to 25 mg/kg (estimated C_{max} 2892 ng/mL[4]; 16 times the clinical C_{max}). No effects of alogliptin on cardiovascular function (including cardiac troponin levels in blood) were seen in repeat-dose toxicity studies in dogs at doses up to 200 mg/kg/day for 39 weeks (approximately 220 times the anticipated clinical C_{max}). Alogliptin (up to 100 mg/kg; resulting in estimated C_{max} values 36 times the clinical C_{max}) had no effect on respiratory parameters in the rat.

No specialised studies were conducted to assess effects on the renal and gastrointestinal systems. In repeat-dose toxicity studies, no effect on urinary parameters, the renal system or gastrointestinal system were seen in rats treated with ≤ 900 mg/kg/day PO alogliptin for 6 months (resulting in approximately 380 times the clinical AUC) or in dogs treated with ≤200 mg/kg/day alogliptin for 9 months (resulting in approximately 230 times the clinical AUC).

Overall, based on animal data, no effects on the cardiovascular, respiratory, renal, gastrointestinal or central nervous systems are predicted during clinical use.

Pharmacokinetics

Absorption was rapid in all animals tested with time to achieve maximum concentrations (T_{max}) ranging from 0.4 (dog) to 2.3 (rat) in single-dose studies and similar values were seen in repeat-dose studies. Bioavailability ranged from moderate, 41% in rats, to high, 85% and 88% in dogs and monkeys, respectively. In rats, alogliptin was absorbed into the portal plasma via the jejunum with little metabolism. Exposure was greater than dose-proportional in rats and dogs at doses greater than 3 mg/kg. Small sex differences were observed in exposure dose-proportionality but these were not significant. Following intravenous (IV) administration, the terminal elimination half-life was relatively short in rats and dogs (range 1–3 h). The half-life in monkeys was notably longer (about6 h) than in rats and dogs. Following repeat-dosing, there was no evidence of accumulation in mice or monkeys. However, some accumulation seemed evident in rats and dogs with repeat oral dosing ≥ 13 weeks.

The volume of distribution was greater than total body water in rats, dogs and monkeys. Consistent with this, tissue distribution of drug-derived radioactivity was rapid and widespread. Radioactivity was either not detected or was detected at very low levels in brain and spinal cord tissues indicating that alogliptin is unlikely to cross the blood brain barrier. Penetration into the testes was observed in rats. Alogliptin appears to have affinity for melanin showing preferential distribution to the eyes, particularly sclera, of pigmented rats. Plasma protein binding was low to moderate in all animal species and humans (< 60%) and concentration-dependence was evident. Partitioning of alogliptin and its metabolites into red blood cells ranged from 23% in rats to 41% in dogs after oral administration of ^{14}C-alogliptin.

With the exception of dogs, the metabolic profile for alogliptin was similar across species tested, with unchanged drug predominating in both *in vitro* and *in vivo* studies. The amount of unchanged drug remaining was highest when human hepatocytes were incubated with alogliptin (96.3% in males, 89.4% in females) and lowest for rat

[3] QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. QTc is the QT interval corrected for heart rate.
[4] Based on data from Study 322/00250 with a 30 mg/kg PO dose

hepatocytes (79.9%). Metabolism of alogliptin was limited, with the formation of 2 primary metabolites, M-I (demethylation) and M-II (acetylation) and very small amounts of other metabolites (formed by hydroxylation and glucuronidation). Cytochrome P450 (CYP) subtype 2D6 (CYP2D6) was shown to have a major role in the formation of M-I, while CYP3A4 was involved in the formation of other metabolites that were not identified. *In vitro*, both enzymes only produced very limited metabolism of alogliptin. The two primary metabolites M-I and M-II were detected in the plasma of all species tested. In humans, exposures (AUC) to the M-I and M-II metabolites of alogliptin were less than 1% and 4%, respectively, of the parent compound. With the exception of rats, the M-II metabolite was more prevalent in humans than in animal species (< 1%). The level of M-I was high in dogs (20–60% of the parent) compared with other animal species (< 3%). Furthermore, a higher level of other metabolites was seen in dogs compared with other species. Alogliptin has one chiral centre. *In vivo* studies evaluating chiral conversion ([*R*]- to [*S*]-enantiomer) indicate that the chiral centre of alogliptin is stable in both rats and dogs.

Excretion of alogliptin and/or its metabolites was predominantly via the faeces in rats and dogs, though urinary excretion was not insignificant. Biliary excretion was demonstrated in rats and dogs. There was evidence of enterohepatic recirculation in rats. Alogliptin is mainly excreted via the urine in humans.

The PK profiles of the animal species used in this submission were sufficiently similar to human PK to allow them to serve as appropriate animal models for the safety evaluation of alogliptin. A similar pattern of rapid absorption, wide distribution and metabolic profile was seen in the animal species and humans. The main route of excretion was one difference between the animals and humans although the urine did account for a significant amount of the excretion in animals.

Pharmacokinetic drug interactions

Alogliptin is unlikely to possess any clinically relevant CYP induction ability. At the highest concentration tested (100 μM) alogliptin was much less effective an inducer of CYP3A4/5 activity than rifampicin. A clinical drug-drug interaction study with midazolam (CYP3A4) did not show any CYP3A4 induction after 7-days dosing of alogliptin.

Alogliptin was able to produce 27% inhibition of CYP2D6 in *in vitro* experiments at high concentrations with an estimated IC_{50} >100 μM. There was no evidence for direct inhibition of CYP1A2, 2C8, 2C9, 2C19, or 3A4/5 with an estimated IC_{50} value greater than 100 μM. There was evidence of metabolism dependent inhibition of CYP3A4/5 with IC_{50} estimates of 78 μM and ≥100 μM for midazolam 1'-hydroxylation and testosterone 6β-hydroxylation, respectively. There was no evidence that alogliptin has the potential to cause metabolism-dependent inhibition of the other CYP enzymes tested (1A2, 2C8, 2C9, 2C19, and 2D6). Compared to the estimated clinical C_{max} (range 154–202 ng/mL, males/females [0.5-0.6 μM]) there is little or no potential of CYP inhibition at the clinical range of concentrations. Taken together with the limited metabolism of alogliptin, pharmacokinetic (PK) drug interactions involving CYP450 enzymes are not predicted.

No definitive studies of alogliptin with transporters were submitted in the original dossier.

In vitro, no metabolic interactions were evident between alogliptin and the thiazolidinedione, rosiglitazone, or the sulfonylureas, glyburide and glipizide. In rats, co-administration with pioglitazone had no effects on the plasma kinetics of alogliptin or its metabolites, M-I and M-II. While co-administration with alogliptin had no effect on the plasma kinetics of pioglitazone itself, exposures to the M-II metabolite of pioglitazone increased with increasing alogliptin doses. Exposure to alogliptin (and its metabolites) in rats appeared to decrease with increasing metformin doses, which was particularly evident with a 10:1 metformin:alogliptin ratio. Co-administration with alogliptin had no apparent effect on metformin exposure.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted in rats (PO and IV dosing) and dogs (PO dosing). The studies were conducted under GLP conditions in accordance with the EU Guideline *Note for guidance on single-dose toxicity* (3BS1a). The observation period (14 days) was appropriate. The maximum non-lethal dose was the maximum tested, 1471 mg/kg PO and 25 mg/kg IV in rats and 368 mg/kg PO in dogs. The estimated exposures (AUC) at the maximum non-lethal oral doses are > 400 times the clinical AUC. Overall, the data indicate a low-order of oral toxicity for alogliptin. The only common clinical sign in rats (≥ 500 mg/kg PO) and dogs (≥ 221 mg/kg PO) was hypoactivity. Additional clinical signs in dogs included reddened skin (≥ 92 mg/kg PO), facial swelling, salivation and emesis (at 368 mg/kg PO). No target organs were identified at necropsy.

Repeat-dose toxicity

Repeat-dose toxicity studies of up to 13 weeks duration were conducted in mice, 26 weeks duration in rats and 39 weeks duration in dogs. The duration of the pivotal studies, which were conducted under GLP conditions, was acceptable given the intended duration of clinical use. The clinical route (PO) was used in all studies. The species chosen were appropriate based on pharmacological (all species) and PK (at least for rodents) considerations. The highest doses resulted in very high exposures (see following table). In addition, repeat oral dose studies were conducted in Cynomolgus monkeys, specifically to assess the potential for skin lesions, a toxicity seen with some other DPP-4 inhibitors. Adequate exposures were achieved in these studies.

Table 1. Relative exposure in selected repeat-dose toxicity and carcinogenicity studies

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio#
Mouse (CD-1)	13 weeks	200	71.1	40
		300	95.7	54
		400	117	66
		600	180	102
	2 years 18 month sample [carcinogenicity]	50	9.7	5.5
		150	42.4	24
		300	89.7	51
Rat (SD)	13 weeks	100	45.0	26
		400	165	94
		1000	605	344
	26 weeks	100	43.9	25
		400	259	147

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio[#]
		900	664	377
	2 years 18 month sample [carcinogenicity]	75	48.2	27
		400	425	241
		800	703	399
Dog (Beagle)	13 weeks	10	8.8	5
		30	35.3	20
		90	124	70
	9 months	30	40.9	23
		100	197	112
		200	400	227
Monkey (Cynomolgus)	13 weeks	3	3.6	2
		10	13.1	7
		30	47.0	27
Human[a]	Day 8	[25 mg]	1.76	–

[#] = animal:human plasma $AUC_{0-24\,h}$; [a]Exposure value from elderly subjects used as most conservative

Major toxicities

Over the range of alogliptin doses tested in mice and dogs there were few major toxic effects. Exposures achieved were up to 100 and 227 times the clinical AUC. In rats, on the other hand, where higher doses were tested, a number of toxicities were seen, with effects on the liver, kidney, testes and lymphoid organs.

Increased liver weights, with centrilobular hypertrophy, were seen in rats treated with ≥ 900 mg/kg/day PO alogliptin (377 times the clinical exposure). This is considered an adaptive rather than toxicological effect. Increased ALP activity was also noted. Increases in other liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) were only seen at high doses (≥ 1666 mg/kg/day PO alogliptin). Given the hepatic effects only occurred at high exposures in a single species, hepatic effects during clinical use are not predicted from animal data.

In rats at doses ≥ 1333 mg/kg/day PO alogliptin (estimated exposure > 400 times the clinical exposure) effects on the urinary bladder and kidney were seen, leading to premature mortality in some animals. These effects occurred at lower doses and with greater frequency in males. Tubular degeneration/regeneration was seen in males at doses ≥ 1333 mg/kg/day but was only seen at 2000 mg/kg/day in females. Tubular dilatation was seen in a small number of animals of both sex at 2000 mg/kg/day. Effects in the urinary bladder were less frequent than effects in the kidney but also occurred with greater frequency in males. The effects in the bladder were inflammation, transitional cell

hyperplasia and haemorrhage at ≥ 1333 mg/kg/day and erosion/ulceration and dilatation at 2000 mg/kg/day. The findings in the urinary bladder are consistent with local irritation caused by alogliptin and/or metabolites. The effects on the kidney and the urinary bladder were not seen at lower doses in rats or in other species at any dose (albeit lower exposures were assessed), and are not expected to be clinically-relevant.

After long-term treatment with alogliptin at ≥ 400 mg/kg/day PO to male rats (resulting in 147 times the clinical exposure), severe, bilateral degeneration/atrophy of seminiferous tubules with severe epididymal oligospermia were evident. While an increase in the percentage of abnormal sperm was seen in male rats at 1000 mg/kg/day PO in the fertility study, there was no effect on functional fertility (see *Reproductive toxicity*, below). Exposure at the no effect level for testicular/epididymal findings was 25. Therefore, these effects are not expected to be clinically-relevant.

Some effects on the lymphoid system were seen in rats at doses ≥ 1000 mg/kg/day (344 times the clinical exposure). These effects were most prominent in the thymus where decreased thymic weights and thymic lymphoid depletion were noted. At doses ≥ 1333 mg/kg/day, lymphoid necrosis was also observed as well as lymphoid depletion of the spleen, and at 2000 mg/kg/day, there was depletion and necrosis of mandibular and mesenteric lymph nodes. Animals given these high doses showed some evidence of poor condition and it is possible that the effects on the lymphoid organs were secondary to this poor condition.

Administration of the other DPP-4 inhibitors vildagliptin and saxagliptin to monkeys has been associated with necrotic skin lesions (Andukuri *et al*., 2009[5]). Alogliptin was tested in Cynomolgus monkeys for 4 and 13 consecutive weeks at doses of up to 30 mg/kg/day PO. No skin lesions were observed at any of the sites examined (thoracic region, tail, left fore- and hind-limbs, left auricle, nasal area, and scrotum). The no observed adverse effect level (NOAEL) in this study was 30 mg/kg/day (about 27 times the clinical AUC).

Reddening of the skin and facial swelling was seen in dogs following single and repeat dosing at doses ≥30 mg/kg (exposure ratio based on AUC (ER_{AUC}) about 20). This finding is reminiscent of a pseudoallergic reaction, though histamine levels were not measured. No such findings were seen in any other species, suggesting dogs were particularly sensitive.

With regard to haematological parameters, some effects were noted in mice and rats, but these were inconsistent and no clear dose-response patterns were apparent. Cholesterol (total and high density lipoproteins (HDL)) was consistently elevated in male and female dogs over the full 39 week dosing period at doses ≥ 30 mg/kg/day (23 times the clinical exposure). Total cholesterol was also elevated in rats at doses ≥ 1333 mg/kg/day.

Overall, the toxicity findings with alogliptin were similar with those of the more specific DPP-4 inhibitors, sitagliptin and linagliptin, rather than the less specific inhibitors, vildagliptin and saxagliptin. No clinically-relevant findings were evident.

Combination studies

Repeat-dose toxicity studies of up to 13 weeks duration were conducted with alogliptin/metformin and alogliptin/pioglitazone combinations to rats. The clinical route (PO) was used in all studies. Rats are considered an appropriate species to assess the toxicity of alogliptin and are a species that has been used previously to assess the toxicity of both pioglitazone and metformin. A parallel alogliptin only control group was not included in either of the pivotal studies.

Alogliptin:metformin dose ratios in the pivotal 13 week study were 1:3 and 1:10. Findings with metformin occurred predominantly in the 1000 mg/kg/day PO metformin group.

[5] Andukuri R, Drincic A, Rendell M (2009). Alogliptin: a new addition to the class of DPP-4 inhibitors. Diabetes, metabolic syndrome and obesity : targets and therapy 2: 117-126.

These included diarrhoea and soft faeces with effects on the gastrointestinal tract evident during post-mortem analyses (diffuse mucosal hyperplasia of the caecum and minimal to mild erosion of the glandular stomach and duodenum). Effects were also seen on the adrenal gland (increased weights correlating with fasciculata cell hypertrophy), heart (increased heart weights with myocardial cell hypertrophy and minimal to mild cardiomyopathy), kidney (tubular cell hypertrophy and tubular cell vacuolation), sublingual and submandibular glands (decreased granules in the glandular duct of both glands and acinar cell hypertrophy and minimal to mild hypertrophy of the ductal epithelium of the submandibular gland), liver (hepatocyte hypertrophy) and pancreas (decreased zymogen granule). When provided in combination with alogliptin (100/1000 mg/kg/day PO alogliptin/metformin) exacerbated effects were seen on the adrenal glands and heart (myocardial cell hypertrophy only). Reduced body weight gain was also evident at 100/1000 mg/kg/day alogliptin/metformin compared with 1000 mg/kg/day metformin only, and is possibly attributed to a pharmacological effect. Exacerbated toxicities were less evident with a 100/300 mg/kg/day PO alogliptin/metformin combination. Exposures from this combination were 13 times and 4 times the clinical exposure of alogliptin and metformin (from a 1000 mg twice daily (bid) metformin hydrochloride dose; Timmins *et al.*, 2005[6]), respectively. No new toxicities were evident with the combination.

Alogliptin:pioglitazone dose ratios in the pivotal 13 week toxicity were 2–8:1. Toxicities observed with pioglitazone only (14.5 mg/kg/day PO) were increased heart weights with an increased incidence of cardiomyopathy in males, and, in both sexes, increased adipose tissue in brown and white fat, corresponding to adipocyte hypertrophy and hyperplasia. No new or exacerbated toxicities were observed when provided in combination with alogliptin (100/14.5 mg/kg/day PO alogliptin/pioglitazone).

Genotoxicity

The potential genotoxicity of alogliptin was assessed in the standard battery of tests: Ames test, forward mutation test in mouse lymphoma cells and a mouse micronucleus assay, conducted according to International Conference on Harmonisation (ICH) guidelines, with definitive tests conducted under GLP conditions. All *in vitro* assays were appropriately validated. While a positive concurrent control was not used in the mouse micronucleus assay, the strain is commonly used in such assays. All assays returned negative results. The highest dose in the mouse micronucleus test (200 mg/kg by intraperitoneal (IP) injection) produced exposures 47 times the clinical AUC. The data indicate that alogliptin has a low genotoxic potential.

Carcinogenicity

Two year carcinogenicity studies were conducted in mice and rats using daily oral dosing. Group sizes were appropriate with adequate survival for a sufficient length of time. The highest doses were acceptable, resulting in exposures >25 times the anticipated clinical exposure (ICH Topic S1C(R2).*Dose Selection for Carcinogenicity Studies of Pharmaceuticals* EMEA/CHMP/ICH/383/1995, April 2008). No drug-related tumours were evident in mice treated with ≤ 300 mg/kg/day PO alogliptin or female rats treated with ≤ 800 mg/kg/day PO alogliptin (51 and about 400 times the clinical exposure, respectively). In male rats, there was a clear dose-related increase in thyroid C-cell lesions (hyperplasia, adenoma and carcinoma). The incidence of tumours (adenomas and carcinomas) was higher than historical control values at doses ≥ 400 mg/kg/day (241 times the clinical exposure) suggesting a likely relationship with drug treatment. The no effect level (NOEL) for

[6] Timmins P, Donahue S, Meeker J, Marathe P. Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clin Pharmacokinet* 2005:44: 721-729.

tumours was 75 mg/kg/day (27 times the clinical exposure). No drug-related tumours have been observed with other DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and linagliptin); however, thyroid C-cell tumours have been commonly observed with GLP-1 agonists (such as liraglutide and exenatide). The mechanism of thyroid C-cell tumours with these agents has been suggested to be due to persistent GLP-1 receptor activation in the thyroid of rodents (see AusPAR for liraglutide (rys) [Victoza]). A similar mechanism may occur with alogliptin, though no mechanistic studies were provided to support this. Nonetheless, given the high exposures at the NOEL (27 times the clinical exposure), the thyroid tumours are not likely to be clinically-relevant.

Reproductive toxicity

The reproductive toxicity of alogliptin was assessed in rats and rabbits in GLP compliant studies. The studies investigated potential effects on male and female fertility in rats, embryofetal toxicity (rats and rabbits) and pre-/postnatal development (rats). Adequate animal numbers were used in the pivotal studies and treatment periods were appropriate. Toxicokinetic data were obtained from animals in the definitive embryofetal studies, while toxicokinetic data for the other studies were extrapolated from the 13 week repeat-dose toxicity study in rats. Exposure levels for alogliptin were significantly greater than the anticipated clinical exposure (see table below).

Table 2. Relative exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio[#]
Rat (SD)	Fertility	100	45	26
		500	303	172
		1000	605	343
	Embryofetal development	250	130	74
		500	311	177
		1000	783	445
Rabbit (NZW)	Embryofetal development	100	86.4	49
		200	257	146
		500	679	386
		700	936	532
Human	–	[25 mg]	1.76	–

[#] = animal:human plasma $AUC_{0-24\,h}$

Fertility was unaffected in rats when males and females were treated with ≤ 500 mg/kg/day PO alogliptin (172 times the clinical AUC). However, at the higher dose of 1000 mg/kg/day PO, a slight increase in the level of abnormal sperm was seen in males, with an increase in oestrus cycle length (by 1 day, but there was no effect on the time to mating) and a slight decrease in the number of implantations was seen in females. As mild effects

on fertility were only seen at extremely high exposures, effects on fertility are not anticipated during clinical use.

Alogliptin and its primary metabolite, M-I, crossed the placenta in rats with exposures similar to those seen in maternal plasma. In both rats and rabbits, adverse embryofetal effects were only evident in the context of maternotoxicity, with small fetal weights and an increase in skeletal abnormalities (bent ribs and reduced ossification) in rats at ≥ 500 mg/kg/day PO alogliptin (exposure ratio based on AUC [ER_{AUC}], 177) and an increase in post-implantation loss and reduced ossification in rabbits at 500 mg/kg/day PO alogliptin (ER_{AUC}, 386). Exposures at the NOAEL in both rats and rabbits (250 mg/kg/day PO and 200 mg/kg/day PO, respectively) were at 74 and 146 times, respectively, the clinical AUC.

Transfer of alogliptin and its metabolites was shown to be high in lactating rats. In a pre- and post-natal study in rats, pups from dams treated with ≥500 mg/kg/day PO (ER_{AUC}, 172), had lower pup birth weights and demonstrated a lower postnatal survival to day 4. Reduced weights were observed into adulthood. Reduced pup weights have been seen in similar studies with other DPP-4 inhibitors. Males from dams dosed at 1000 mg/kg/day suggested some behavioural effects (increased motor activity and impaired learning). This was not seen in females. The age of vaginal patency (which is positively correlated with body weight) was delayed in female offspring from dams dosed at 1000 mg/kg/day. No other effects on offspring behavioural and developmental parameters were noted.

Combination embryofetal toxicity studies

Rat embryofetal toxicity studies were conducted with alogliptin/pioglitazone and alogliptin/metformin combinations. Parallel single agent groups were included in the pivotal alogliptin/metformin study; however, there was no alogliptin control group in the alogliptin/pioglitazone study. This is not considered to affect the ability to interpret the results of the study.

Alogliptin:pioglitazone dose ratios ranged from 30:40 to 100:40. Relative to vehicle only control groups, an increased incidence of supernumerary coronary ostium and dilatation of the renal pelvis and ureter (the latter considered to be due to growth retardation) was seen in fetuses from rats that received a 100/40 mg/kg/day PO alogliptin/pioglitazone combination. Only the incidence of supernumerary coronary ostium was significantly higher than that seen in the 40 mg/kg/day PO pioglitazone only group. Co-administration with alogliptin was considered to potentiate the effects of pioglitazone alone in terms of fetal growth and visceral variations.

Alogliptin:metformin dose ratios in the pivotal study were 1:1.5 and 1:5. In fetuses from rats that received 100/500 mg/kg/day PO alogliptin/metformin, an increased incidence of fetal abnormalities was seen compared with either agent alone. These abnormalities included small eye bulge (correlating with microphthalmia), cleft palate, microglossia, mandibular micrognathia, misshapen tail, absent sacral vertebra and reduced ossification. The malformations did not occur in the presence of maternal hypoglycaemia and were not associated with any PK interactions. However, they were restricted to 2 dams, one of which showed significant toxicity. While the higher incidence may be incidental, a possible synergistic effect of alogliptin and metformin on fetal damage cannot be dismissed. The NOAEL for these effects was 100/150 mg/kg/day PO alogliptin/metformin, resulting in exposures 29 and 3 times the clinical exposure to alogliptin and metformin[7], respectively.

[7] Data from Timmins *et al.* (2005) where a value of 20.5 µg.h/mL is reported for a 1000 mg bid administration of an immediate release form of metformin.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1.[8] Given the increase in post-implantation loss in rabbits and other effects at high alogliptin doses in rats and rabbits, Category B3[9] is considered more appropriate. This pregnancy category is also consistent with other DPP-4 inhibitors. However, as alogliptin is intended to be used with other anti-diabetics, the pregnancy category for these agents also needs to be considered.

Local tolerance

Incubation of alogliptin (2.5 mg/mL) with human blood did not cause haemolysis. Incubation of alogliptin (2.5 mg/mL) with human plasma did not cause any macroscopic flocculation, precipitation, or coagulation. Local tolerance studies of the same formulation were assessed in rabbits following IV and paravenous injection. Local changes following IV injection were unremarkable, while slight subcutaneous haemorrhage was seen following paravenous injection.

Phototoxicity

Alogliptin appears to have affinity for melanin showing preferential distribution to the eyes, particularly sclera, of pigmented rats. No effects on the eyes of dogs were reported in the pivotal repeat-dose study. Possible phototoxic effects of alogliptin were directly investigated in hairless mice. Mice were exposed to daily UV radiation (4 days) following single oral doses up to 800 mg/kg. There was no evidence of skin erythema, oedema or flaking was seen, indicating that the phototoxic potential of alogliptin is low.

Paediatric use

Alogliptin is not intended to be used in paediatric patients. Nonetheless, two repeat-dose toxicity studies were conducted in juvenile rats (age of 4 weeks at the commencement of dosing). No unusual toxicities were seen in either sex at doses ≤ 300 mg/kg/day PO for 4 weeks. The 8 week study was conducted to assess effects on the developing male reproductive system. No adverse effects on this system were evident at doses ≤ 300 mg/kg/day PO. There was no significant difference in exposure (AUC) to alogliptin in rats aged 4, 8 or 12 weeks. However, exposure (AUC) to M-I and M-II appeared to be higher in rats aged 12 weeks compared with those aged 4 weeks.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for alogliptin detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the Nonclinical Evaluator with one exception: the thyroid tumours identified in males in the rat carcinogenicity study should be included in the safety specification.

[8] Use in pregnancy Category B1 is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.*

[9] Use in pregnancy Category B3 is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*

Nonclinical summary and conclusions

- The overall quality of the nonclinical dossier was good with all pivotal studies conducted according to GLP.
- *In vitro*, alogliptin inhibited DPP-4 (various sources) with IC_{50} values of approximately 7 nM. Alogliptin showed no measurable inhibition of any other members of the DASH family of serine proteases and tryptase tested.
- Oral administration of alogliptin to mice, rats, dogs, and monkeys effectively inhibited plasma DPP-4 activity. In animal models of diabetes, alogliptin produced improvements in diabetic parameters (glucose tolerance, insulin levels, glucose levels, glycosylated haemoglobin levels and pancreatic morphology). Interactions of alogliptin with other anti-diabetic agents (pioglitazone, voglibose, metformin and glibenclamide) were also examined on diabetic indices in animal models of diabetes. The effects of the combinations of the drugs were generally additive but the following synergistic effects were seen: alogliptin and pioglitazone mediated increases in pancreatic insulin content and the insulinogenic index in db/db mice; alogliptin and voglibose mediated increases in pancreatic insulin and plasma intact GLP-1 levels in *db/db* mice; alogliptin and metformin mediated increases in intact plasma GLP-1 levels and insulin secretion in Wistar fatty rats.

  Primary pharmacology studies in animal models of T2DM support the use of alogliptin for the proposed indication. No studies assessed the combination of alogliptin with insulin.
- Alogliptin had minimal to no activity on other enzymes or receptors at clinically-relevant concentrations. Alogliptin did not have any notable effects on CNS, cardiovascular or respiratory function in rats or dogs following oral administration.

  Clinically significant off-target activities are unlikely based on the results of secondary pharmacology studies
- Overall, the PK profile in animals was qualitatively similar to that of humans. Alogliptin was readily and rapidly absorbed with a similar T_{max} in all species. Half-life values were similar in rats and dogs but longer in monkeys and humans. Plasma protein binding of alogliptin was low to moderate in all animal species and humans. Tissue distribution of alogliptin was wide but penetration into brain and spinal cord was very limited. Alogliptin appears to have affinity for melanin. With the exception of dogs, metabolism of alogliptin is minimal to low in all species. Drug-related material was excreted via urine and faeces with urine as the predominant route of excretion in humans while faeces predominated for animal species.
- Pharmacokinetic drug interactions involving CYP enzymes are unlikely.
- Alogliptin had a low order of acute oral toxicity in rats and dogs.
- Repeat-dose toxicity studies were performed in mice, rats and dogs. High relative exposures were achieved in these studies. The pivotal studies were of 6 months duration in rats and 9 months duration in dogs. Clinical signs of a pseudoallergic reaction were seen in dogs; however no major organ toxicities were seen in this species or in mice. A range of alogliptin-related histopathological changes in the kidneys and urinary bladder, liver, testes and lymphoid organs were only seen at high relative exposures (> 100) in rats. No skin lesions were seen in Cynomolgus monkeys treated for 13 weeks at doses resulting in exposures 27 times the clinical AUC.

  No major organ toxicities were observed with alogliptin in mice or dogs. Histopathological changes in the kidneys and livers of rats are not considered clinically-relevant based on large safety margins.

- Repeat-dose toxicity studies of up to 13 weeks duration were conducted with alogliptin/pioglitazone and alogliptin/metformin combinations to rats. No new or exacerbated toxicities were noted with alogliptin/pioglitazone combinations. While no new toxicities were seen with alogliptin/metformin combinations, exacerbated effects were seen in the adrenal gland (fasciculate cell hypertrophy) and heart (myocardial cell hypertrophy).
- The potential genotoxicity of alogliptin was investigated in a standard battery of tests. The results were negative in all tests and alogliptin is unlikely to pose a mutagenic or clastogenic risk to humans.
- No treatment related increase in tumour incidence was observed in mice or female rats in 2-year oral carcinogenicity studies. An increase in the incidence of thyroid C-cell hyperplasia, benign adenomas and malignant carcinomas was seen in male rats at high relative exposures (240 times the clinical AUC). Relative exposure at the NOEL was 27.

  Alogliptin is unlikely to pose a genotoxic or carcinogenic hazard to patients.
- Fertility was unaffected in rats at doses resulting in approximately 170 times the clinical AUC. Perturbations to oestrous cycling and effects on sperm were seen at higher doses. Placental transfer of alogliptin and its metabolites was demonstrated in rats, with some reductions in fetal body weights and effects on ossification seen in rats and rabbits. Alogliptin and its metabolites were excreted in milk and decreased postnatal weight gain was seen in rats. Some developmental effects were seen in male offspring of rat dams exposed to high doses (about 340 times the clinical AUC).
- Rat embryofetal toxicity studies were conducted with alogliptin/pioglitazone and alogliptin/metformin combinations. Potentiation of fetal effects was seen with alogliptin/pioglitazone, while a possible synergistic effect on fetal damage was seen with alogliptin/metformin.

  Effects on reproductive parameters with alogliptin occurred at sufficiently high exposures to be not of particular concern. Fetal effects with alogliptin/pioglitazone and alogliptin/metformin combinations have uncertain clinical relevance.
- No effects on the developing male reproductive system were seen in juvenile rat studies.
- Alogliptin was not phototoxic in hairless mice at high doses.

Recommendation

There are no nonclinical objections to the registration of alogliptin for the proposed indication.

Revisions to nonclinical statements in the draft PI were recommended. Details of these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor has provided the following rationale for the development of alogliptin:

> Type 2 diabetes mellitus is a chronic condition resulting from three distinct deficiencies: impaired insulin secretion, insulin resistance and hypersecretion of glucagon. T2DM is associated with a number of long-term microvascular and macrovascular complications. The United Kingdom Prospective Diabetes Study Group (UKPDS, 1999[10]) showed that the risk of microvascular complications was dramatically reduced among patients with T2DM when a glycosylated haemoglobin (HbA1c) target level of < 7% was achieved. Current pharmacologic interventions for T2DM include a diverse range of antidiabetic medications with different mechanisms of action including insulin and insulin analogues, sulfonylureas (SU), biguanides such as metformin (MET), meglitinides, thiazolidinediones (TZDs), inhibitors of alpha-glucosidase, analogues of glucagon-like peptide-1 (GLP-1), DPP-4 inhibitors, and synthetic analogues of human amylin. Despite the variety of antidiabetic medications, many patients have difficulty achieving an HbA1c target level of <7% due to side effects, restricted use, long-term tolerability issues, or compliance issues resulting from side effects, route of administration, and pill burden. During the first 3 years of monotherapy with a first-line oral antidiabetic medication, up to 50% of patients exhibit inadequate glycaemic control (Inzucchi, 2002[11]). As an added complication, the progressive nature of T2DM makes it difficult to maintain glycaemic control with traditional agents and generally necessitates the escalation of drug doses and the use of combination therapies. Upon failure of monotherapy, combination therapy is initiated, typically with a second (and sometimes third) oral antidiabetic agent, with or without insulin (Inzucchi, 2002).

There are several DPP-IV inhibitors currently approved for the treatment of T2DM in Australia, including linagliptin, saxagliptin and sitagliptin.

Overseas regulatory activity

Alogliptin was not registered in the US at the time this application was submitted to Australia. An application was lodged in the US on 27th December 2007 but the FDA required a Cardiovascular Safety Study to be conducted in accordance with FDA Guidance for Industry: *Diabetes Mellitus- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. A reapplication was lodged on 25th July 2011 but the FDA had identified a potential signal for hepatic safety with alogliptin, precluding approval of alogliptin products at that time. The FDA has requested additional post-marketing data from outside the US as well as additional clinical data to provide reassurance of the hepatic safety profile. The sponsor planned to lodge a further application in July 2012 that would include the same data package as submitted in EU and planned for Australia. However, it is not explicitly stated in the Australian dossier the type of data requested by the FDA (and specifically whether this includes details of potential cases of drug induced liver injury) and whether such data are included in the Australian dossier.

[10] UK Prospective Diabetes Study (UKPDS) Group Intensive blood-glucose control with sulphonylureas or insulin. compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–53.
[11] Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes. *JAMA* 2003:287;360-372.

Formulation

A different formulation was used in the Phase II and Phase III studies to that intended for marketing in Australia. Bioequivalence was demonstrated for these formulations.

Scope of the clinical dossier

The dossier represents a full development program for a new medical entity. The submission contained the following clinical information:

- 28 clinical pharmacology studies, including 28 that provided PK data and five that provided PD data.
- One population PK analysis.
- Nine pivotal efficacy/safety studies, including:
  - Three as add on to MET: Study SYR-322-MET-008, Study SYR-322-MET-302, Study SYR-322-305
  - One as add-on to SU: Study SYR-322-SULF-007
  - Two as add-on to TZD: Study SYR-322-TZD-009, Study 01-06-TL-322OPI-002
  - Two as monotherapy: Study SYR-322-PLC-010, Study SYR-322-303
  - One as add-on to insulin: Study SYR-322-INS-011

  There were no studies that used other DPP-IV inhibitors as comparators.
- One dose-finding study: Study SYR-322-003
- Ten other efficacy/safety studies: Study SYR-322-301; Study 01-05-TL-322OPI-001; Study 01-06-TL-322OPI-004; Study SYR-322-OLE-012; Study SYR-322-308; Study SYR-322-CCT-001/ Study SYR-322-OCT-001; Study SYR-322-CCT-003/ Study SYR-322-OCT-003; Study SYR-322-CCT-004/ Study SYR-322-OCT-004; Study SYR-322-CCT-005/ Study SYR-322-OCT-005 (SU); Study SYR-322-CCT-006/ Study SYR-322-OCT-005 (MET)
- Three safety studies: Study SYR-322-402, Study SYR-322-004 and Study SYR-322-019
- Three Periodic Safety Update Reports (PSURs), an Integrated Summary of Efficacy, and an Integrated Summary of Safety

The sponsor also provided a Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical studies presented in the dossier are stated to have been, and appear to have been, conducted according to good clinical practice.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each PK topic.

Table 3. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Main objective of the study
PK in healthy adults			
General PK-	-Single dose	Study SYR-322-103	Absolute bioavailability
		Study SYR-322-001	Ascending dose
		Study SYR-322/CPH-001	Metabolism
		Study SYR-322/CPH-002	Metabolism
		Study SYR-322-014	Mass balance
	-Multi-dose	Study SYR-322-101	
Bioequivalence† -	Single dose	Study SYR-322-027	Commercial formulation
	Food effect	Study SYR-322-026	25 mg dose
		Study SYR-322/CPH-006	
		Study SYR-322-CPH-007	
		Study SYR-322-005	
PK in special populations			
Target population§	-Single dose -Multi-dose	None	
		Study SYR-322-002	Target population PK
	Hepatic impairment	Study SYR-322-023	Hepatic impairment
	Renal impairment	Study SYR-322-006	Renal impairment
	Neonates/infants/ children/ adolescents	None	
	Elderly	Study SYR-322-022	General PK
		Study SYR-322/CPH-003	General PK
Genetic/ gender-related PK			
	Males versus females	Study SYR-322-022	General PK

PK topic	Subtopic	Study ID	Main objective of the study
PK interactions			
	MET, cimetidine	Study SYR-322-005	Interaction
	caffeine, tolbutamide, dextromethorphan, midazolam, fexofenadine	Study SYR-322-015	Interaction
	ketoconazole, fluconazole, gemfibrozil	Study SYR-322-016	Interaction
	Pioglitazone	Study SYR-322-017	Interaction
	Gliburide	Study SYR-322-018	Interaction
	Cyclosporin	Study SYR-322-020	Interaction
	Warfarin	Study SYR-322-021	Interaction
	Ethynyl oestradiol, norethindrone	Study SYR-322-024	Interaction
	Atorvastatin	Study SYR-322-025	Interaction
	Digoxin	Study SYR-322-029	Interaction
	Voglibose	Study SYR-322/CPH-004	Interaction
Population PK analyses			
	Healthy subjects	None	
	Target population	Study SYR-322-met-008-002342-1	

None of the PK studies had deficiencies that excluded their results from consideration.

Summary of pharmacokinetics in the target population

In subjects with T2DM, in the dose range 25 mg to 400 mg once daily for 14 days, there was dose proportionality for area under the concentration-time curve over time zero to 24 h (($AUC_{0\text{-}24\,h}$) and C_{max} (Study SYR-322-002; see Table 4). The mean (90% confidence interval (CI)) accumulation ratio for $AUC_{0\text{-}24\,h}$ was 1.34 (1.28 to 1.40) and for C_{max} it was 1.09 (0.99 to 1.21). Apparent clearance (CL) after oral administration (CL/F) ranged from 10.43 L/h to 16.11 L/h. Renal CL ranged from 9.93 L/h to 15.23 L/h. The fraction excreted unchanged in urine ranged from 60.8% to 63.4%. The coefficient of variation (CV%) for CL/F ranged from 22% to 32%, the CV% for apparent volume of distribution (V) after oral administration (V/F) ranged from 26% to 41%. V/F ranged from 286.7 L to 299.0 L.

Table 4. Summary of alogliptin pharmacokinetics in the target population. Study SYR-322-002

Parameter	25 mg		100 mg		400 mg	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
AUC_{0-24} (ng•h/mL)						
n	13	13	14	14	15	14
Mean	1058	1474	4917	6804	15823	20675
CV%	16	15	24	42	26	28
Min	733.2	1178	3785	4567	9758	11384
Max	1359	1739	8156	15708	23807	30492
C_{max} (ng/mL)						
n	13	13	14	14	15	14
Mean	145.5	152.8	629.9	741.8	2420	2560
CV%	40	25	44	78	47	31
Min	68.70	98.10	331.0	349.0	1090	1350
Max	286.0	220.0	1250	2610	5480	4090
T_{max} (h)						
n	13	13	14	14	15	14
Median	1.25	1.05	1.30	1.03	1.03	1.13
Min	0.75	0.75	0.48	0.55	0.50	0.50
Max	6.23	4.53	6.37	10.58	2.52	4.50
$t_{1/2,z}$ (h)						
n	-	10	-	11	-	14
Mean	-	21.13	-	20.24	-	12.50
CV%	-	41	-	74	-	18
Median	-	19.58	-	15.94	-	12.30
Min	-	11.79	-	11.57	-	9.74
Max	-	38.55	-	64.67	-	17.53
CL/F (L/h)						
n	-	10	-	11	-	14
Mean	-	10.43	-	11.09	-	16.11
CV%	-	22	-	25	-	32
Min	-	6.85	-	6.62	-	10.39
Max	-	13.56	-	15.24	-	28.89
V_z/F (L)						
n	-	10	-	11	-	14
Mean	-	299.0	-	292.9	-	286.7
CV%	-	26	-	41	-	31
Min	-	210.6	-	186.7	-	169.1
Max	-	410.3	-	618.0	-	478.9

Evaluator's overall conclusions on pharmacokinetics

Alogliptin has been characterised as having rapid and complete oral absorption and predictable renal excretion. There were few significant drug interactions.

Because alogliptin is predominantly cleared renally dose adjustment in renal failure would be necessary. The dosing regimen proposed by the sponsor is appropriate for this.

There was no study of renal excretion or re-absorption. This could be provided from the data already available if renal clearance of unbound drug were related to glomerular filtration rate.

Pharmacodynamics

Studies providing pharmacodynamic data

There were five studies that contribute PD data:

- Study SYR-322-CPH-007
- Study SYR-322-001
- Study SYR-322/CPH-001
- Study SYR-322/CPH-002
- Study SYR-322-002

There were no clinical studies on mechanism of action.

Primary pharmacodynamic effects in the target population

In subjects with T2DM, in the alogliptin dose range 25 mg to 400 mg once daily for 14 days, there was little difference in DPP-IV inhibition between the 25 mg dose, the 100 mg dose and the 400 mg dose (Study SYR-322-002). AUC for plasma glucose was lowest in the 100 mg group. AUC for plasma insulin was greatest in the 100 mg group. The 4 h postprandial glucose concentrations decreased from baseline, in comparison with placebo, to Day 14 by least squares (LS) mean -39.9 (standard error (SE) of the mean 14.42) mg/dL in the 25 mg group, -48.6 (SE 14.71) mg/dL in the 100 mg group and -68.3 (SE, 15.08) mg/dL in the 400 mg group. HbA1c changed, in comparison with placebo, by a mean (SE) of -0.27% (0.129%) in the 25 mg group, -0.45% (0.128%) in the 100 mg group and -0.32% (0.131%) in the 400 mg group.

Evaluator's overall conclusions on pharmacodynamics

The proposed dosing regimen is supported by the PD data. Near maximal DPP-IV inhibition is achieved by the 25 mg dose level over a 24 hour dosing interval.

Efficacy

Studies providing efficacy data

Nine pivotal efficacy studies were provided:

- Alogliptin in combination with MET
  - Study SYR-322-MET-008: a multicentre, randomised, double blind, placebo controlled, three treatment arm study to assess the efficacy and safety of two dose levels of alogliptin in combination with MET versus MET alone
  - Study SYR-322-MET-302: a multicentre, randomised, double blind, placebo controlled study to determine the efficacy and safety of alogliptin plus MET, alogliptin alone, or MET alone in subjects with T2DM
  - Study SYR-322-305: a multicentre, randomised, double blind, active controlled study to evaluate the durability of the efficacy and safety of alogliptin compared to glipizide when used in combination with MET in subjects with T2DM (a 52 week interim report was provided)
- Alogliptin in combination with sulfonylurea
  - Study SYR-322-SULF-007: a multicentre, randomised, double blind, placebo controlled, three treatment arm study to assess the efficacy and safety of two dose levels of alogliptin in combination with a sulfonylurea versus a sulfonylurea alone
- Alogliptin in combination with a thiazolidinedione
  - Study SYR-322-TZD-009: a multicentre, randomised, double blind, placebo controlled, three treatment arm study to assess the efficacy and safety of two dose levels of alogliptin-in combination with pioglitazone (with or without MET or a SU) versus pioglitazone alone (with or without MET or a SU)
  - Study 01-06-TL-322OPI-002: a multicentre, randomised, double blind, four treatment arm study in subjects with T2DM who have failed treatment with diet and exercise, to assess efficacy and safety of alogliptin in combination with pioglitazone as compared with either alogliptin or pioglitazone alone
- Alogliptin as monotherapy

  - Study SYR-322-PLC-010: a multicentre, randomised, double blind, placebo controlled study to determine the efficacy and safety of alogliptin compared with placebo in subjects with T2DM
  - Study SYR-322-303: a multicentre, randomised, double blind, comparator controlled study to evaluate the efficacy and safety of alogliptin monotherapy compared to glipizide in elderly subjects with T2DM

- Alogliptin in combination with insulin
  - Study SYR-322-INS-011: a multicentre, randomised, double blind, placebo controlled, three arm study to evaluate the efficacy and safety of two dose levels of alogliptin in combination with insulin (with or without MET) versus insulin alone (with or without MET)

In addition, 10 supportive efficacy studies and an Integrated Analysis of Efficacy using data pooled from various studies and subgroups were provided.

Evaluator's conclusions on clinical efficacy in T2DM

Alogliptin 12.5 mg and 25 mg were superior to placebo as add-on therapy in subjects on stable doses of MET (Study SYR-322-MET-008). The LS mean difference (95% CI) (treatment versus placebo) was -0.50 (-0.68 to -0.32) % for the 12.5 mg dose and -0.48 (-0.67 to -0.30) % for the 25 mg dose ($p < 0.001$). The benefit was maintained for 26 weeks.

Alogliptin 12.5 mg and MET 500 mg or 1000 mg twice daily were superior to the individual components as monotherapy, and to placebo (Study SYR-322-MET-302). The treatment differences were:

- Alogliptin 12.5mg / MET 500 mg twice daily was superior to alogliptin 12.5 mg twice daily: LS mean difference (97.5% CI) -0.67 (-0.96 to -0.37) %, $p < 0.001$
- Alogliptin 12.5 mg / MET 1000 mg twice daily was superior to alogliptin 12.5 mg twice daily: LS mean difference (97.5% CI) -1.00 (-1.29 to -0.71) %, $p < 0.001$
- Alogliptin 12.5 mg / MET 500 mg twice daily was superior to MET 500 mg twice daily: LS mean difference (97.5% CI) -0.57 ((-0.87 to -0.27) %, $p < 0.001$
- Alogliptin 12.5 mg / MET 1000 mg twice daily was superior to MET 1000 mg twice daily: LS mean difference (97.5% CI) -0.44 (-0.73 to -0.16) %, $p < 0.001$
- There was no significant difference between alogliptin 12.5 mg twice daily and alogliptin 25 mg once daily: LS mean difference (95% CI) -0.04 (-0.30 to 0.22), $p = 0.759$
- Alogliptin 12.5 mg / MET 500 mg twice daily was superior to placebo: LS mean difference (95% CI) -1.37 (-1.63 to -1.11) %, $p < 0.001$
- Alogliptin 12.5 mg / MET 1000 mg twice daily was superior to placebo: LS mean difference (95% CI) -1.70 (-1.96 to -1.45)%, $p < 0.001$

The treatment benefit was maintained for 52 weeks.

Alogliptin was not inferior to glipizide in subjects on stable doses of MET (Study SYR-322-305). In comparison with glipizide/MET:

- Alogliptin 25 mg/MET was not inferior: LS mean difference (upper 98.75% CI) -0.09 (-0.004)
- Alogliptin 12.5 mg/MET was not inferior: LS mean difference (upper 98.75% CI) -0.10 (-0.002)

The non-inferiority comparison was made at Week 52 of treatment.

Alogliptin 12.5 mg and 25 mg were superior to placebo in subjects on stables doses of SU (Study SYR-322-SULF-007). The LS mean difference (95% CI) (treatment versus placebo) was -0.39 (-0.59 to -0.19) % for the 12.5 mg dose and -0.53 (-0.73 to -0.33) % for the 25 mg dose ($p < 0.001$). The benefit was maintained for a minimum of 26 weeks.

Alogliptin 12.5 mg and 25 mg were superior to placebo as add-on therapy in subjects on stable doses of TZD, with or without concomitant treatment with MET or SU (Study SYR-322-TZD-009). The LS mean difference (95% CI) (treatment versus placebo) was -0.47 (-0.67 to -0.28) % for the 12.5 mg dose and -0.61 (-0.80 to -0.41) % for the 25 mg dose ($p < 0.001$). The treatment benefit was maintained for 26 weeks.

Alogliptin 12.5 mg and 25 mg in combination with pioglitazone was superior to alogliptin alone, or pioglitazone alone (Study 01-06-TL-322OPI-002). The LS mean difference (95% CI) alogliptin 12.5 mg/pioglitazone versus pioglitazone was -0.40 (-0.63 to -0.18) %, $p<0.001$; for alogliptin 25 mg/pioglitazone versus pioglitazone was -0.56 (-0.78 to -0.33) %, $p < 0.001$; and for alogliptin 25 mg/pioglitazone versus alogliptin 25 was -0.75 (-0.98 to -0.53) %, $p < 0.001$. The treatment benefit was maintained for 26 weeks.

Alogliptin 12.5 mg and 25 mg as monotherapy were superior to placebo (Study SYR-322-PLC-010). The LS mean difference (95% CI) (treatment versus placebo) was -0.54 (-0.76 to -0.31) % for the 12.5 mg dose and -0.57 (-0.80 to -0.35) % for the 25 mg dose ($p < 0.001$). The treatment benefit was maintained for 26 weeks.

Alogliptin 25 mg was not inferior to SU (glipizide) in monotherapy: LS mean difference (upper 97.5% CI) -0.05 (0.13) %, i.e. the upper confidence limit for the LS mean difference was less than +0.4% (Study SYR-322-303). Non-inferiority was demonstrated after 52 weeks of treatment. There were fewer hypoglycaemic episodes with alogliptin than with SU.

Alogliptin 12.5 mg and 25 mg were superior to placebo as add-on treatment in subjects treated with insulin (Study SYR-322-INS-011). The LS mean difference (95% CI) (treatment versus placebo) was -0.51 (-0.72 to -0.30) % for the 12.5 mg dose and -0.59 (-0.80 to -0.37) % for the 25 mg dose ($p < 0.001$). The treatment benefit was maintained for 26 weeks.

Alogliptin appeared to interact with SU and TZD in increasing body weight. However, there did not appear to be an adverse effect on weight in monotherapy or in combination with MET.

Overall, efficacy was demonstrated in subjects aged ≥ 65 years in comparison with placebo. Efficacy was independent of gender, race or baseline HbA1c.

The study populations included in the pivotal studies were similar to those for which alogliptin is intended for marketing in Australia. The concomitant and comparator treatments are also widely available and used in Australia. The clinical endpoints used in the efficacy studies were appropriate as were the statistical methods used to test the hypotheses. The treatment effect was both clinically and statistically significant.

Safety

Studies providing evaluable safety data

Safety data were available from all the efficacy studies discussed above. In addition there were three studies that assessed safety variables as a primary outcome: one cardiovascular safety study (Study SYR-322-402) and two thorough QT studies (Study SYR-322-004 and Study SYR-322-019).

In addition, an Integrated Analysis of Safety using data pooled across various studies and subgroups, and 3 (post-market) Periodic Safety Update Reports (PSURs) covering the period from 16th April 2010 to 15th October 2011 (during the time alogliptin was approved in Japan) were provided.

Patient exposure

In Phase II and Phase III controlled trials there were a total of 2476 subjects treated with alogliptin 12.5 mg once daily (with 468 treated for more than one year) and 3749 with alogliptin 25 mg, (with 678 treated for more than one year) (Table 5). There were 1144 subjects treated with alogliptin that were aged 65 to 74 years, 140 aged 75 to 84 years and one aged ≥ 85 years. There were 1916 subjects treated with alogliptin with mild renal impairment (Cockroft-Gault glomerular filtration rate (GFR) ≥ 60 and < 90 mL/min/1.73 m^2); 279 with moderate renal impairment (Cockroft-Gault GFR ≥ 30 and < 60 mL/min/1.73 m^2) and two subjects with severe renal impairment (Cockroft-Gault GFR <30 mL/min/1.73 m^2).

Table 5. Exposure by Dose and Duration of Dosing Phase II and III Controlled-Study Pool (IAS)

	Alogliptin 12.5 mg (N = 2476)	Alogliptin 25 mg (N = 3749)	All Alogliptin (N = 6354)
Duration of Exposure (days) [1]			
n	2476	3749	6354
Mean (SD)	214.4 (101.59)	219.2 (105.55)	214.2 (105.25)
Median	182.0	183.0	182.0
Min, Max	1, 402	1, 393	1, 402
Duration of Exposure (categorized), n (%) [1]			
<=1 day	3 (0.1%)	6 (0.2%)	9 (0.1%)
>1 day - <7 days	5 (0.2%)	12 (0.3%)	18 (0.3%)
>=7 days - <30 days	80 (3.2%)	129 (3.4%)	237 (3.7%)
>=30 days - <6 months	380 (15.3%)	614 (16.4%)	1094 (17.2%)
>=6 months - <12 months	1355 (54.7%)	1989 (50.4%)	3244 (51.1%)
>=12 months	653 (26.4%)	1099 (29.3%)	1752 (27.6%)
>=351 days	645 (26.1%)	1090 (29.1%)	1735 (27.3%)
>=365 days	468 (18.9%)	678 (18.1%)	1146 (18.0%)

	Placebo (N = 793)	Active Comparator (N = 2257)	All Comparators (N = 3050)
Duration of Exposure (days) [1]			
n	793	2257	3050
Mean (SD)	141.8 (53.80)	247.3 (116.92)	219.9 (114.07)
Median	179.0	210.0	183.0
Min, Max	1, 210	1, 407	1, 407
Duration of Exposure (categorized), n (%) [1]			
<=1 day	1 (0.1%)	6 (0.3%)	7 (0.2%)
>1 day - <7 days	1 (0.1%)	10 (0.4%)	11 (0.4%)
>=7 days - <30 days	46 (5.8%)	87 (3.9%)	133 (4.4%)
>=30 days - <6 months	290 (36.6%)	368 (16.3%)	658 (21.6%)
>=6 months - <12 months	455 (57.4%)	791 (35.0%)	1246 (40.9%)
>=12 months	0	995 (44.1%)	995 (32.6%)
>=351 days	0	987 (43.7%)	987 (32.4%)
>=365 days	0	642 (28.4%)	642 (21.0%)

Post-marketing safety data: cumulative patient exposure was estimated to be 117,359 patient-years since approval. In addition, cumulative exposure to a fixed dose alogliptin-pioglitazone product was estimated to be 7,215 patient-years in Japan.

Evaluator's overall conclusions on clinical safety

The overall pattern and frequency of treatment emergent adverse events (TEAEs) was similar for alogliptin and placebo or comparator. There was no significant difference in the frequency of TEAEs between the 12.5 mg dose and the 25 mg dose. The pattern of treatment related TEAEs reflected that of concomitant medications (for example, gastrointestinal for MET and hypoglycaemia for SU). There did not appear to be a specific

pattern of adverse drug reactions (ADRs) for alogliptin. Death was uncommon and serious adverse events (SAEs) did not appear to occur in a greater frequency than with comparator or placebo. Discontinuations due to AEs did not appear to occur at greater frequency with alogliptin than placebo or comparator, and was not dose related.

Elevation of hepatic enzyme ALT did not appear to occur at greater frequency with alogliptin than with placebo or comparator.

QTc prolongation of regulatory interest did not occur at therapeutic doses or at 100 mg daily (four times the recommended dose), but did occur at 400 mg once daily after a week. This dose level is 16 times the proposed dose.

Hypoglycaemia was uncommon with alogliptin and was related to co-medication with SU or insulin. The incidence of hypoglycaemia was lower than with SU in monotherapy.

There were subjects reported with acute pancreatitis with alogliptin, but the overall incidence of elevated lipase was no greater than with comparator or placebo.

First round benefit-risk assessment

First round assessment of benefits

Alogliptin 12.5 mg and 25 mg were superior to placebo as add-on therapy in subjects on stable doses of MET (Study SYR-322-MET-008). The LS mean difference (95% CI) (treatment versus placebo) was -0.50 (-0.68 to -0.32) % for the 12.5 mg dose and -0.48 (-0.67 to -0.30) % for the 25 mg dose ($p < 0.001$). The benefit was maintained for 26 weeks.

Alogliptin 12.5 mg and MET 500 mg or 1000 mg twice daily was superior to the individual components as monotherapy, and to placebo (Study SYR-322-MET-302). The treatment differences were:

- Alogliptin 12.5mg / MET 500 mg twice daily was superior to alogliptin 12.5 mg twice daily: LS mean difference (97.5% CI) -0.67 (-0.96 to -0.37) %, $p < 0.001$
- Alogliptin 12.5mg / MET 1000 mg twice daily was superior to alogliptin 12.5 mg twice daily: LS mean difference (97.5% CI) -1.00 (-1.29 to -0.71) %, $p < 0.001$
- Alogliptin 12.5mg / MET 500 mg twice daily was superior to MET 500 mg twice daily: LS mean difference (97.5% CI) -0.57 (-0.87 to -0.27) %, $p < 0.001$
- Alogliptin 12.5mg / MET 1000 mg twice daily was superior to MET 1000 mg twice daily: LS mean difference (97.5% CI) -0.44 (-0.73 to -0.16) %, $p < 0.001$
- There was no significant difference between alogliptin 12.5 mg twice daily and alogliptin 25 mg once daily: LS mean difference (95% CI) -0.04 (-0.30 to 0.22), $p = 0.759$
- Alogliptin 12.5mg / MET 500 mg twice daily was superior to placebo: LS mean difference (95% CI) -1.37 (-1.63 to -1.11) %, $p < 0.001$
- Alogliptin 12.5mg / MET 1000 mg twice daily was superior to placebo: LS mean difference (95% CI) -1.70 (-1.96 to -1.45)%, $p < 0.001$

The treatment benefit was maintained for 52 weeks.

Alogliptin was not inferior to glipizide in subjects on stable doses of MET (Study SYR-322-305). In comparison with glipizide/MET:

- Alogliptin 25 mg/MET was not inferior: LS mean difference (upper 98.75% CI) -0.09 (-0.004)

- Alogliptin 12.5 mg/MET was not inferior: LS mean difference (upper 98.75% CI) -0.10 (-0.002)

The non-inferiority comparison was made at Week 52 of treatment.

Alogliptin 12.5 mg and 25 mg were superior to placebo in subjects on stables doses of SU (Study SYR-322-SULF-007). The LS mean difference (95% CI) (treatment versus placebo) was -0.39 (-0.59 to -0.19) % for the 12.5 mg dose and -0.53 (-0.73 to -0.33) % for the 25 mg dose ($p < 0.001$). The benefit was maintained for a minimum of 26 weeks.

Alogliptin 12.5 mg and 25 mg were superior to placebo as add-on therapy in subjects on stable doses of TZD, with or without concomitant treatment with MET or SU (Study SYR-322-TZD-009). The LS mean difference (95% CI) (treatment versus placebo) was -0.47 (-0.67 to -0.28) % for the 12.5 mg dose and -0.61 (-0.80 to -0.41) % for the 25 mg dose ($p < 0.001$). The treatment benefit was maintained for 26 weeks.

Alogliptin 12.5 mg and 25 mg in combination with pioglitazone was superior to alogliptin alone, or pioglitazone alone (Study 01-06-TL-322OPI-002). The LS mean difference (95% CI) alogliptin 12.5 mg/pioglitazone versus pioglitazone was -0.40 (-0.63 to -0.18) %, $p<0.001$; for alogliptin 25 mg/pioglitazone versus pioglitazone was -0.56 (-0.78 to -0.33) %, $p <0.001$; and for alogliptin 25 mg/pioglitazone versus alogliptin 25 was -0.75 (-0.98 to -0.53) %, $p <0.001$. The treatment benefit was maintained for 26 weeks.

Alogliptin 12.5 mg and 25 mg as monotherapy were superior to placebo (Study SYR-322-PLC-010). The LS mean difference (95% CI) (treatment versuss placebo) was -0.54 (-0.76 to -0.31) % for the 12.5 mg dose and -0.57 (-0.80 to -0.35) % for the 25 mg dose ($p <0.001$). The treatment benefit was maintained for 26 weeks.

Alogliptin 25 mg was not inferior to SU (glipizide) in monotherapy: LS mean difference (upper 97.5% CI) -0.05 (0.13) %, that is, the upper confidence limit for the LS mean difference was less than +0.4% (Study SYR-322-303). Non-inferiority was demonstrated after 52 weeks of treatment. There were fewer hypoglycaemic episodes with alogliptin than with SU.

Alogliptin 12.5 mg and 25 mg were superior to placebo as add-on treatment in subjects treated with insulin (Study SYR-322-INS-011). The LS mean difference (95% CI) (treatment versus placebo) was -0.51 (-0.72 to -0.30) % for the 12.5 mg dose and -0.59 (-0.80 to -0.37) % for the 25 mg dose ($p <0.001$). The treatment benefit was maintained for 26 weeks.

Alogliptin appeared to interact with SU and TZD in increasing body weight. However, there did not appear to be an adverse effect on weight in monotherapy or in combination with MET.

Overall, efficacy was demonstrated in subjects aged ≥ 65 years in comparison with placebo. Efficacy was independent of gender, race or baseline HbA1c.

The study populations included in the pivotal studies were similar to those for which alogliptin is intended for marketing in Australia. The concomitant and comparator treatments are also widely available and used in Australia. The clinical endpoints used in the efficacy studies were appropriate as were the statistical methods used to test the hypotheses. The treatment effect was both clinically and statistically significant.

The proposed dosing regimens, and the indications sought by the sponsor, are supported by the efficacy and clinical pharmacology data presented in the submission.

First round assessment of risks

The overall pattern and frequency of TEAEs was similar for alogliptin and placebo or comparator. There was no significant difference in the frequency of TEAEs between the

12.5 mg dose and the 25 mg dose. The pattern of treatment related TEAEs reflected that of concomitant medications (such as gastrointestinal for MET and hypoglycaemia for SU). There did not appear to be a specific pattern of ADRs for alogliptin. Death was uncommon and SAEs did not appear to occur in a greater frequency than with comparator or placebo. Discontinuations due to AEs did not appear to occur at greater frequency with alogliptin than placebo or comparator, and was not dose related.

Elevation of ALT did not appear to occur at greater frequency with alogliptin than with placebo or comparator.

QTc prolongation of regulatory interest did not occur at therapeutic doses or at 100 mg daily (four times the recommended dose), but did occur at 400 mg once daily after a week. This dose level is 16 times the proposed dose.

Hypoglycaemia was uncommon with alogliptin and was related to co-medication with SU or insulin. The incidence of hypoglycaemia was lower than with SU in monotherapy.

Acute pancreatitis has been reported with alogliptin, but in the Integrated Analysis of Safety the overall incidence of elevated lipase was no greater than with comparator or placebo. It is not clear whether the risk of pancreatitis is greater, or lesser, than other DPP-IV inhibitors.

First round assessment of benefit-risk balance

Although the treatment benefit of alogliptin, both as add-on therapy and monotherapy, is clinically significant and adequately demonstrated, there remain some safety concerns. The risk of drug induced liver injury requires further review, and consideration should be given to deferring the decision on approval pending the decision of the FDA (see *Overseas regulatory activity* above).

First round recommendation regarding authorisation

The data submitted in the dossier support the requested indication:

> *Add-on combination:*
>
> *Nesina / Vipidia is indicated to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, metformin and a thiazolidinedione, or insulin (with or without metformin).*
>
> *Initial combination:*
>
> *Nesina / Vipidia is indicated for use as initial combination with metformin to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control and dual alogliptin and metformin therapy is appropriate.*

Specifically, the data support the individual components of the requested indication. These components are:

- Add-on therapy as:
  - Dual therapy with a SU, a TZD or MET
  - Triple therapy with a TZD and a SU or MET
  - Triple/dual therapy with insulin with or without MET
- Initial combination therapy:

– Initial combination therapy with MET

However, the decision on marketing authorisation should be deferred pending the decision of the FDA with regard to the risk of drug induced liver injury with alogliptin (see *Overseas regulatory activity* above).

Clinical questions

Pharmacokinetics

Is there any evidence for net renal excretion or reabsorption? What is the renal clearance of free (unbound) alogliptin in relation to creatinine clearance?

Efficacy

The sponsor should provide summary tabulations of the reasons for exclusion of subjects from the PPS for Study SYR-322-303 and Study SYR-322-305.

Safety

What are the details of the FDA concerns regarding hepatic safety and which data have been provided by the Sponsor in response?

The Sponsor should provide a tabulation of all cases of potential drug induced liver injury, and all cases satisfying the criteria of Hy's Law.[12]

Second round evaluation of clinical data submitted in response to questions

· *Is there any evidence for net renal excretion or re-absorption? What is the renal clearance of free (unbound) alogliptin in relation to creatinine clearance?*

Data provided by the sponsor in response to this question indicate significant net renal excretion of alogliptin by an unknown mechanism.

· *The sponsor should provide summary tabulations of the reasons for exclusion of subjects from the PPS for Study SYR-322-303 and Study SYR-322-305.*

The sponsor provided these summary tabulations for Study SYR-322-303, and for Study SYR-322-305 has provided directions as to where the tabulation is in the dossier.

In Study SYR-322-303 there were more subjects in the glipizide group excluded because of shorter duration of therapy than in the alogliptin: 44 (20.1%) subjects compared with 33 (14.9%) respectively.

In Study SYR-322-305 the reasons for exclusion, and proportions of subjects excluded, were similar for the three treatment groups.

These data do not change the conclusions with regard to efficacy.

· *What are the details of the FDA concerns regarding hepatic safety and which data have been provided by the Sponsor in response?*

In their initial review of the alogliptin dossier the FDA had identified an imbalance in the proportion of subjects with elevated liver enzymes. The sponsor states that the initial FDA dossier did not include data from Study SYR-322-305.

[12] Hy's law is a set of criteria, based on altered liver function, used to predict whether a drug is at high risk of causing drug induced liver injury

The sponsor has provided a summary tabulation of subjects with elevations in liver enzymes for the Phase II and III studies from the studies initially submitted to the FDA. Overall, there were more subjects with marked elevation in ALT (> 5 x upper limit of normal (ULN)) in the alogliptin treated groups: 17 (0.3%) subjects compared with three (0.1%) in the comparator. However, for other measures of liver injury there were similar proportions in the alogliptin and comparator groups.

On 26th July 2012 the sponsor provided further data to the FDA and an updated summary table of these data was provided by the sponsor. This still indicates a slight imbalance in the proportion of subjects with ALT > 5 x ULN: 34 (0.35%) subjects in the alogliptin groups, corresponding to 0.49 per hundred patient years exposure, compared with 17 (0.29%) in the placebo, corresponding to 0.39 per hundred patient years exposure.

At the request of the FDA the sponsor also provided data from Study SYR-322_402, in January 2013. There were 19 (0.80%) subjects in the alogliptin group and twelve (0.51%) in the placebo with ALT > 5 x ULN.

- *The Sponsor should provide a tabulation of all cases of potential drug induced liver injury, and all cases satisfying the criteria of Hy's Law.*

The sponsor has provided tabulations of cases satisfying the biochemical criteria of Hy's Law for the Phase II and III studies and the post-marketing data. In addition the sponsor has provided a tabulation of subjects with potential drug induced liver injury from the post-marketing data.

There were five subjects exposed to alogliptin in clinical trials that developed ALT/AST > 3 × ULN with concurrent total bilirubin > 2 × ULN. Of these five cases three were serious but all had alternative explanations.

There were eight serious post-marketing cases of ALT/AST > 3 × ULN with concurrent total bilirubin >2 × ULN. One case was associated with pancreatitis. One case was associated with progression of pancreatic cancer. One case did not appear to have an alternative explanation. The remaining five cases had alternative explanations.

There were six post-marketing cases of potential drug induced liver injury. All six had alternative explanations.

The sponsor also convened an independent panel of five hepatologists that made the following findings:

> "We independently reviewed each of the 13 subjects experiencing ALT > 10 x ULN during the first 120 days blinded to treatment allocations using the Drug Induced Liver Injury Network (DILIN) methodology. None of these cases was considered by any of us to have a "definite" (> 95% probability), or "highly likely" (75-94% probability) causal link to alogliptin treatment. Only two cases were considered by any of us to have a causality grade of "probable". For one case a causal relationship to study drug was considered "probable" by one expert but "possible" (25-50% probability) by the other four hepatologists. This subject carried a diagnosis of hemochromatosis and experienced an asymptomatic spike in aminotransferases that resolved despite continued treatment with study drug. There was only one case where a causal relationship to study drug was considered "probable" by all five experts. This patient apparently also experienced an asymptomatic aminotransferase elevation that resolved with discontinuation of study drug treatment. It should be noted that potentially important information, such as viral serologies, is not available for this case. Both cases were receiving alogliptin treatment; neither had evidence of liver dysfunction.

> We found no Hy's Law cases in the clinical trials database (that is, cases with ALT > 3 x with total bilirubin > 2 x and alkaline phosphatase < 2 x or R value[13] > 5 in whom other potential causes were excluded by adequate investigation)."

With regard to post-marketing data the panel found:

> "We reviewed eight cases of potential concern reported from Japan, the only country with post-marketing experience with alogliptin. Each of us independently assessed causality in these cases according to the DILIN methodology. No cases were deemed "definite" (>95% probability) or "highly likely" (75-94% likely). Three of the eight cases were deemed "probable" (50-74% probability), four were deemed "possible" (25-49% probability) and one case could not be assessed due to insufficient data. Two probable cases met the criteria for Hy's law designation, one of whom was recovering from liver failure when she developed pneumonia and died. No characteristic or "signature" presentation could be discerned among the 8 cases reviewed."

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of alogliptin in the proposed usage are unchanged from those identified in the *First round assessment of benefits*, above.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of alogliptin in the proposed usage are unchanged from those identified in *First round assessment of risks,* above. The additional data supplied by the sponsor, whilst reassuring, do not exclude a potential association between alogliptin and drug induced liver injury.

Second round assessment of benefit-risk balance

The benefit-risk balance of alogliptin, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

The data submitted in the dossier support the requested indication:

Add-on combination:

> *Nesina / Vipidia is indicated to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, metformin and a thiazolidinedione, or insulin (with or without metformin).*

Initial combination:

[13] The type of liver injury at DILI onset is classified as hepatocellular, cholestatic or mixed by the R ratio, which compares ALT and alkaline phosphatase levels in multiples of their upper limit of normal (ULN) based upon the first available values after DILI onset. The R ratio is calculated by the formula R = (ALT/ULN)/(alkaline phosphatase/ULN). Patients with acute hepatocellular injury have R > 5 (Fontana RJ *et al*. Drug-Induced Liver Injury Network (DILIN) Prospective Study. *Drug Safety* 2009; 32(1): 55–68.

Nesina / Vipidia is indicated for use as initial combination with metformin to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control and dual alogliptin and metformin therapy is appropriate.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (Alogliptin EU-RMP (version 1.0, dated 05 April 2012) + Australian-specific Annex (ASA, version 1.0, dated July 2012)) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 6):

Table 6. Summary of the Ongoing Safety Concerns

Important Potential Risks	· Hypersensitivity Reactions · Pancreatitis
Important Missing Information	· Patients with concurrent cardiovascular disease · Patients with severe renal impairment or end-stage renal disease (ESRD) requiring dialysis. · Patients with severe hepatic impairment · Pregnant or lactating women. · Children and adolescents. · Use in clinical practice.

Pharmacovigilance plan

A summary of the pharmacovigilance activities proposed by the sponsor is provided in Table 7:

Table 7. Summary of the proposed pharmacovigilance activities

Important Potential Risks	
Hypersensitivity Reactions	Routine pharmacovigilance Targeted follow-up questionnaires Analysis of ongoing and planned clinical trial safety data Drug utilisation study (DUS) in the Netherlands Prescription Event Monitoring study (PEMS) in the

Important Potential Risks	
	UK
Pancreatitis	Routine pharmacovigilance Targeted follow-up questionnaires Analysis of ongoing and planned clinical trial safety data DUS in the Netherlands PEMS in the UK
Important Missing Information	
Patients with concurrent cardiovascular disease	Routine pharmacovigilance Analysis of clinical trial safety data from the ongoing cardiovascular (CV) outcome study 402. DUS in the Netherlands PEMS in the UK
Patients with severe renal impairment or ESRD requiring dialysis	Routine pharmacovigilance Analysis of clinical trial safety data from the ongoing cardiovascular (CV) outcome study 402.
Patients with severe hepatic impairment	Routine pharmacovigilance
Pregnant or lactating women	Routine pharmacovigilance DUS in the Netherlands PEMS in the UK
Children and adolescents	Routine pharmacovigilance Analysis of safety data from planned clinical studies in paediatrics in line with the Paediatric Investigational Plan. DUS in the Netherlands PEMS in the UK
Use in clinical practice	Routine pharmacovigilance DUS in the Netherlands PEMS in the UK

Risk minimisation activities

Routine risk minimisation (product labelling) is proposed to mitigate the risks associated with alogliptin. No additional risk minimisation activities are proposed.

Summary of RMP evaluation

The following table (Table 8) summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses

Table 8. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Summary of sponsor's response	OPR evaluator's comment
1. It is recommended that the Delegate, implement EU RMP Version 1.0 dated 05 April 2012, including Australian Specific Annex Version 1.0 dated July 2012, and any future updates as a condition of registration.	*The current EU RMP (Version 3.0), submitted to the EMA in March 2013, is included along with the updated ASA annex (Version 2.0) and Risk Management System Changes Version 1.0 to Version 3.0.*	The evaluator recommended implementation of the updated version.
2. It is recommended that the sponsor include elevations in liver enzymes and serious hepatic adverse events as important potential risks in the ongoing safety concerns associated with alogliptin. In addition, adequate and appropriate pharmacovigilance and risk minimisation activities should be proposed for these risks.	*These potential risks have been addressed in the current EU RMP (Version 3.0).*	Hepatotoxicity has been added as an important potential risk. This is acceptable.
3. It is recommended the sponsor include hypoglycaemia as an important identified risk in the ongoing safety concerns associated with alogliptin. In addition, adequate and appropriate pharmacovigilance and risk minimisation activities should be proposed for this risk.	*The data from the Controlled Phase II and III Study Group presented in the initial application does not show an increased risk of hypoglycemia with alogliptin 25 mg (3.6%) compared to placebo (6.2%) or active comparator (12.9%). Note that the alogliptin 25 mg group included subjects taking concomitant antidiabetic therapies.* *Thus, hypoglycemia is not considered an identified risk with alogliptin when administered in combination with antidiabetic agents. Specifically, alogliptin does not increase the incidence of hypoglycemia when administered as dual therapy with agents not known to cause hypoglycemia (for example, metformin, thiazolidinedione). In addition, when alogliptin was administered as dual therapy with an*	Hypoglycaemia is a recognised risk of some antidiabetic medications including insulins and sulphonylureas. As the proposed application seeks an add-on indication with these products it is considered appropriate that the real-world possibility of hypoglycaemia with these combinations is at least considered in the RMP. Therefore it is recommended that 'hypoglycaemia when used in combination with suphonylureas or insulin' is added as an important identified risk. Addition of this risk was also supported by the Advisory

Recommendation in RMP evaluation report	Summary of sponsor's response	OPR evaluator's comment
	antidiabetic agent known to cause hypoglycemia (that is, sulfonylurea [Study 007]), the incidence of hypoglycemia was actually lower in the alogliptin 25 mg group compared to placebo. *In summary, alogliptin overall was not associated with hypoglycaemia and this is reflected in the current EU RMP (Version 3.0). This approach has been discussed and agreed with the EMA during the Day 120 Response process and is also proposed for Australia.*	Committee on the Safety of Medicines (ACSOM) at its meeting in March 2013. Routine pharmacovigilance and risk minimisation would be acceptable.
4. It is recommended that the sponsor provide information on how the proposed Prescription Event Monitoring Study (PEMS) and Drug Utilization study (DUS) to be conducted in the EU will be affected if market authorisation (both PEM and Drug Utilization studies) and funding (for the PEM study) are delayed/not approved in there including details for any alternative pharmacovigilance activities. The sponsor should provide justification that adequate sample size and statistical power will be achieved to monitor and further inform the assigned safety concerns if market authorisation and funding are delayed/not approved in the EU. It is also recommended that the sponsor provide a full protocol/study synopsis and study milestones for reporting for the Drug Utilization Study to the TGA within 3 months of approval (if achieved) of this submission.	*It was suggested by the European Committee for Medicinal Products for Human Use (CHMP) in the alogliptin Day 120 assessment report that the DUS and modified PEM study are no longer necessary given that off-label use of alogliptin is not a safety concern based on the postmarketing experience of other DPP-4 inhibitors available in Europe. Therefore, these studies are no longer proposed and have been removed from the revised RMP (Version 3.0).* *To further investigate the risk of hepatotoxicity with alogliptin, a comprehensive assessment is planned for the final analysis of Study SYR-322-402.*	According to the sponsor the CHMP suggested that the DUS and PEMS were no longer necessary. The sponsor should provide the rationale for this decision. The absence of a PEMS and DUS, in terms of the pharmacovigilance plan is a concern. According to the original RMP the stated objective of the PEMS was "to quantify the incidence of frequently and rarely reported events and to generate signals for potential adverse drug reactions including previously unrecognised adverse drug reactions". This objective remains valid for all safety concerns and is particularly important given the potential liver adverse effects. Therefore it is recommended to the Delegate that the sponsor undertake a study or studies that appropriately act as additional pharmacovigilance to meet the

Recommendation in RMP evaluation report	Summary of sponsor's response	OPR evaluator's comment
		objective stated above. Ideally this should occur in Australia. This recommendation is supported by the advice from the ACSOM at its meeting in March 2013. Further it is recommended that such a requirement is imposed as a condition of registration.
5. It is recommended the sponsor provide details of the five FDA post-marketing studies to the TGA as soon as available. That is, study synopses/full protocols including assigned ongoing safety concerns, study design, inclusion/exclusion criteria, outcomes measurements (primary and secondary), follow-up timepoints, sample size/power calculation and study milestones, should be provided.	*Takeda currently has 2 ongoing studies and protocols were included in this response for both ongoing studies: SYR-322-402, the CV outcomes study and SYR-322-104, the pharmacokinetic paediatric study. In addition, there are 2 planned paediatric studies: Takeda proposes to submit the final protocols to TGA for Study SYR-322-307 and SYR-322-309 in August/September 2015.* *Regarding the fifth "study" referred to in the request, Takeda agreed to conduct a postmarketing requirement (PMR) with the FDA related to the assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions in patients treated with alogliptin. For clarification, a study protocol is not being developed for this PMR, but rather a description of the processes and procedures that will be utilized to support the enhanced pharmacovigilance activities. Takeda and the FDA will be discussing this PMR in the coming months with an agreement expected to be reached by the end of October 2013.*	It is considered that any additional pharmacovigilance or risk minimisation activities undertaken in America as part of the PMR should be broadly applicable in the Australian context. Thus, when these activities are agreed with the FDA they should be described in the alogliptin ASA.

RMP summary and conclusions

It was considered that the sponsor's response to the recommendations raised above has adequately addressed all of the issues identified in the RMP evaluation report with the exception of three outstanding issues which should be addressed:

Issues in relation to the RMP

It is recommended that 'hypoglycaemia when used in combination with suphonylureas or insulin' is added as an important identified risk.

Given the PEMS and DUS have been removed from the RMP the evaluator and ACSOM consider that there is a need for additional pharmacovigilance activities to monitor the frequency of adverse events and identify safety signals for alogliptin. This is particularly important given the possibility of serious liver reactions but also important for the other safety concerns. Therefore it is recommended to the Delegate that the sponsor should conduct a study or studies that appropriately meet these objectives, ideally in Australia. It is suggested that such a requirement is imposed as a condition of registration.

Once agreed with the FDA the sponsor should outline the details of the Post-marketing Requirements (PMR) in the US including how they apply to the Australian context. This should be detailed in a future update to the ASA.

Comments on the safety specification of the RMP

- **Clinical Evaluation Report**

  The clinical evaluator has provided the following comments:

  Drug induced liver injury has been reported in subjects treated with alogliptin and has been cited as the reason for the FDA declining approval for alogliptin. Hence this issue should be included in the RMP as an Important Potential Risk.

OPR Evaluator comment: Hepatotoxicity has since been included as an important potential risk in the revised RMP.

- **Non-clinical evaluation Report**

  The non-clinical evaluator has provided the following comments:

  Results and conclusions drawn from the nonclinical program for alogliptin detailed in the sponsor's draft Risk Management Plan are in general concordance with those of the Nonclinical Evaluator with one exception: the thyroid tumours identified in males in the rat carcinogenicity study should be included in the safety specification.

Key changes to the updated RMP

In their response to the OPR recommendations the sponsor provided an updated RMP (version 3, date 13 March 2013) and Australian-specific Annex (April 2013). Key changes from the version evaluated at Round 1 are summarised below:

Table 9. Key updates in the RMP

Safety specification	· Hypersensitivity and pancreatitis have been elevated to identified risks rather than potential risks (RMP Version 3.0, Section 1.5.2). · Hepatotoxicity, peripheral necrotic skin lesions, gastrointestinal disorders and infections have been added to the RMP as potential risks (RMP Version 3.0, Section 1.5.3). · Malignancies have been added to the RMP as important missing information (RMP Version 3.0, Section 1.3.6). · The missing information "use in clinical practice" has been removed from the RMP as it is not related to any specific safety concern.
Pharmacovigilance activities	The DUS and PEMS have been removed as pharmacovigilance activities.
Risk minimisation activities	No significant changes.

Apart from the removal of the DUS and PEMS, the evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

OPR recommendations

- Implement RMP (version 3, date 13 March 2013) with Australian Specific Annex (April 2013) and any future updates as a condition of registration.
- It is recommended that the sponsor rectify the three outstanding issues listed above.
- It is recommended that the requirement for additional pharmacovigilance activities, in the absence of the PEMS and DUS, is imposed as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

This is an application to register Nesina/Vipidia oral tablets containing 6.25, 12.5 or 25 mg alogliptin (as benzoate) for the following therapeutic indication(s):

Add-on combination

Alogliptin is indicated to improve glycaemic control in adult patients (≥18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, metformin and a thiazolidinedione, or insulin (with or without metformin)

Initial combination

Alogliptin is indicated for use as initial combination with metformin to improve glycaemic control in adult patients (≥18 years old) with type 2 diabetes mellitus

when diet and exercise do not provide adequate glycaemic control and dual alogliptin and metformin therapy is appropriate.'

The proposed alogliptin dose is 25 mg daily irrespective of food. For patients with moderate and severe renal impairment/end stage renal disease (ESRD), a lower dose is recommended (12.5 mg and 6.25mg once daily, respectively). No dose adjustment is proposed in mild renal impairment or mild to moderate hepatic impairment. No clinical experience is currently available in severe hepatic impairment.

Alogliptin is a DPP-4 inhibitor. Four oral DPP-4 inhibitors (linagliptin; saxagliptin; sitagliptin; vildagliptin) and 3 parenteral GLP-1 agonists (liraglutide; exenatide; lixisenatide) are currently approved for marketing in Australia.

The submission comprised full clinical development program.

Alogliptin was approved in Japan in 2010 and in the US in January 2013 for the following indication:

Monotherapy and Combination Therapy

Nesina is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings [see Clinical Studies].

Limitation of Use

Nesina should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Quality

Alogliptin is BCS Class I (high solubility, high permeability). The drug is soluble over the full physiological pH range.

The finished drug products are immediate-release, unscored, film-coated tablets for oral administration, containing 8.5, 17.0, and 34.0 mg alogliptin benzoate, equivalent to 6.25, 12.5, and 25.0 mg alogliptin. The labelling refers to the base content.

The absolute bioavailability of the tablets is nearly 100%. The tablets to be registered were shown to be bioequivalent to the tablets used in Phase III clinical trials. Food effect was not significant.

The submission was considered by the PSC at its 150th meeting in March 2013. Post-PSC the quality related aspects have been satisfactorily resolved. There is no objection in respect of chemistry, manufacturing and controls to the registration of these products from the Module 3 evaluators. The PSC, however, also made the following observations:

- That the data in relation to clearance versus creatinine clearance were not consistent (population PK).
- There was concern about p-glycoprotein interactions in relation to more sensitive drugs.
- Advised that the absence of data on half-maximal effective concentration (EC_{50}) makes it hard to predict concentration over a 24 h period.

The sponsor was requested to provide, in its response to this Overview, comment in relation to these aspects and any clinical impact due to these factors.

Nonclinical

Alogliptin is potent, highly selective, reversible, competitive inhibitor of DPP-4, the enzyme responsible for degradation of incretin hormones such as GLP-1 and GIP.

The nonclinical dossier was of satisfactory quality with all pivotal studies conducted according to GLP. The animal testing was extensive and adequately covered all aspects including repeat-dose toxicity, genotoxicty, carcinogencity and reproductive studies. Alogliptin combination with insulin was not studied. Overall, there are no nonclinical objections to the registration of alogliptin for the proposed indication.

Clinical

The clinical dossier included 28 PK/PD studies including bioavailability/bioequivalence studies, drug interaction studies, studies in special population and population PK analysis. There was one dose ranging study and 7 pivotal clinical efficacy studies (3 add-on to metformin; 1 add-on to SU; 2 add-on to TZD; 1 add-on to insulin). The dossier also included 2 studies of alogliptin as monotherapy (not a requested indication). There were 10 supporting efficacy/safety studies including uncontrolled, long-term extensions of pivotal studies and 3 primary safety studies (2 Thorough QT studies; one CV outcomes study). Post market data (3 PSURs) were also included. Comparison with other DPP-4 antagonists was not studied.

Pharmacokinetics

Pharmacokinetics were studied in both healthy and T2DM patients. Alogliptin is rapidly absorbed from the gastrointestinal tract with near complete bioavailability. There is no clinically relevant food effect. The PK are linear and dose proportional in the 6.25-200 mg range with no significant accumulation. T_{max} is 1-2 h. Plasma protein binding is low (20%) with consequent large apparent volume of distribution (Vd; median 410 L). The excretion is predominantly via renal route as unchanged drug (variously up to 78%). The hepatic metabolism is negligible. Two minor metabolites have been identified and are excreted with urine and faeces. Total body clearance (CL/F) ranged from 10.4 L/h to 16.1 L/h. Renal CL ranged from 9.9 L/h to 15.2 L/h. Terminal half life is about 21 h.

Renal clearance of alogliptin (approximately 170 mL/min) exceeds GFR (120 mL/min) indicating active renal excretion. *In vitro* studies showed that alogliptin was not a substrate for organic anion transporters (OAT1, OAT3 and OCT2) indicating net renal excretion by an unknown mechanism.

Systemic exposure was not altered to significant extent in moderately severe hepatic impairment. The fraction excreted unchanged in urine was 60-65% in normal renal function (creatinine clearance (CrCl) > 80 mL/min), 60% in mild renal impairment (CrCl 51-80 mL/min), 53% in moderate renal impairment (CrCl 30-50 mL/min) and 24% in severe renal impairment (CrCl < 30 mL/min).

Population PK analysis of once daily orally alogliptin in T2DM patients was based on data from a Phase III trial (12.5 mg or 25 mg once daily dosing) in combination with metformin. Two blood samples (one trough, one non-trough) were obtained from each patient (n = 398). A total of 52 (6.2%) measurements from 23 (5.8%) patients were excluded as outliers. A total of 788 alogliptin measurements from 375 patients were used in modelling. Missing covariate data were imputed using prior or subsequent observations, or the population median. Alogliptin concentrations below the level of quantification were excluded from the analysis. Covariates where more than 10% of the data were missing were excluded from the analysis. The final model estimated the population mean CL/F as 17.8 L/h and apparent Vd/F as 187 L. The final model predicted a 15% reduction in CL/F

in patients with mild renal impairment and 30% reduction in alogliptin CL/F in patients with moderate renal impairment compared to T2DM patients with normal renal function.

A number of PK interactions were investigated: metformin (no effect), pioglitazone (10% higher alogliptin exposure), fluconazole (no effect), ketoconazole (15% higher alogliptin exposure), gemfibrozil (12% higher alogliptin exposure), cyclosporin (13% higher alogliptin exposure), atorvastatin (no effect), digoxin (no effect) and voglibose (24% lower alogliptin exposure). Effect of alogliptin on the PK of other drugs was studied for cimetidine (no effect), caffeine (no effect), tolbutamide (no effect), dextromethorphan (26% higher exposure), midazolam (7% higher exposure), fexofenadine (33% higher exposure), pioglitazone (no effect), gliburide (15% higher C_{max}), warfarin (no effect), ethinyloestradiol (no effect), endogenous leutinising hormone (LH); follicle stimulating hormone (FSH); oestrogen (E2); progesterone; sex hormone binding globulin (SHBG; no effect), atorvastatin (14% higher exposure) and digoxin (no effect).

Pharmacodynamics

The maximum effect was shown to be 92% inhibition of DPP-4 activity at 12.5 mg alogliptin dose and 96% inhibition at 25 mg dose. Time to maximal effect was approximately 1.5 h. Peak inhibition of DPP-4 activity (E_{max}) exceeded 93% across all alogliptin dose levels with median time to peak inhibition ranging from 2 to 3 h.

In T2DM patients, in the dose range 25 mg to 400 mg once daily for 14 days, there was little difference in DPP-4 inhibition between the 25 mg, 100 mg and 400 mg dose. The AUC for plasma glucose was lowest in the 100 mg group. The AUC for plasma insulin was greatest in the 100 mg group.

Near maximal DPP-4 inhibition was achieved by the 25mg dose level over a 24 h dosing interval. The inhibition of DPP-4 was also similar for the two dosing regimens (12.5 mg twice daily and 25mg once daily).

Clinical efficacy

Seminal efficacy outcomes from the main studies are presented in tabular format in Table 10 below.

All Phase III, pivotal, controlled studies were carried out in adult patients with poorly controlled T2DM. All were randomised, double blind, controlled (placebo (in combination with existing treatment) or active controlled trials).

These include, among others, 4 main studies (SYR-322-MET-008 (008; use with metformin), SYR-322-SULF-007 (007; use with a sulphonylurea), SYR-322-TZD-009 (009; use with a thiazolidinedione) and SYR-322-INS-011 (011; use with insulin). These were 26 week, parallel-group studies in which alogliptin 12.5 mg and 25 mg once daily was investigated. All studies had 2:2:1 randomisation for 12.5 mg, 25 mg and placebo groups respectively except in Study 011 where 1:1:1 randomisation was used. All studies were designed to include a run-in period of 4 weeks on placebo prior to randomisation followed by 26-week treatment period.

All participants were T2DM patients with inadequate glycaemic control (HbA1c between 7% and 10%) prior to randomisation. In general patients were required to have serum creatinine < 177 µmol/L. Patients with severe heart failure (New York Heart Association (NYHA) class III/IV) or significant cardiovascular disease were excluded.

The Study SYR-322-003 (Study 003) was a dose-ranging, study SYR-322-PLC-010 (Study 010) an absolute effect against placebo and Study SYR-322-MET-302 (Study 302) initial combination use study. Longer term data (52 weeks) were available from Studies SYR-322-305 (305; with metformin; ongoing) and SYR-322-303 (303; monotherapy versus SU;

elderly population). For other longer term experience including uncontrolled extension and longer-term experience with TZD see the Extract from the Clinical Evaluation Report (CER) at Attachment 2 of this AusPAR.

Table 10. Main efficacy trials (randomised, double blind) with main outcomes; adult patients with poorly controlled T2DM; alogliptin = once daily unless otherwise specified; CFB = change from baseline

Study 003 (N=265); dose ranging; treatment-naive patients or on MET, SU or MET/SU; 12 weeks	HbA1c% (CFB) Treatment Difference vs. Placebo	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 12 weeks	
6.25mg ALO	-0.18	-0.9	19.0%	
12.5mg ALO	-0.52	-0.8	47.6%	
25.0mg ALO	-0.55	-2.0	26.7%	
50mg ALO	-0.42	-1.4	37.2%	
100mg ALO	-0.50	-1.6	40.9%	
Placebo		-1.3	14.6%	
Study 010 (N=329); monotherapy vs. placebo; absolute treatment effect; 26 weeks	HbA1c% (CFB) Treatment Difference [95%CI] vs. Placebo	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 26 weeks	BW kg (CFB)
12.5mg ALO	-0.54 [-0.76, -0.31]	-0.57	47.4%	-0.09
25.0mg ALO	-0.57 [-0.80, -0.35]	-0.91	44.3%	-0.22
Placebo		0.63	23.4%	0.18
Study 303 (N=441); monotherapy vs. active; relative effect; elderly population; 52 weeks.	HbA1c% (CFB)	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 52 weeks	BW kg (CFB)
25.0mg ALO	-0.14%	-0.135	48.8%	-0.62
Glipizide 5mg	-0.09%	-0.234	45.3%	0.60
Study 008 (N=527); add-on to metformin; absolute treatment effect in patients on metformin; 26 weeks	HbA1c% (CFB) Treatment Difference [95%CI] vs. Placebo	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 26 weeks	BW kg (CFB)
12.5mg ALO/MET	-0.50 [-0.68, -0.32]	-1.04	51.6%	-0.39
25.0mg ALO/MET	-0.48 [-0.67, -0.30]	-0.96	44.4%	-0.67
Placebo/MET		0.0	18.3%	-0.39
Study 302 (N=784); add-on to metformin; supportive study; initial combination; 26 weeks			HbA1c% (CFB) Treatment Difference [95%CI]	
12.5mg ALO BD	vs.	12.5mgALO /500mg MET BD	-0.67 [-0.96, -0.37]	
500mg MET BD	vs.	12.5mg ALO/500mg MET BD	-0.57 [-0.87, -0.27]	
12.5mg ALO BD	vs.	12.5mg ALO/1000mg MET BD	-1.00 [-1.29, -0.71]	
1000mg MET BD	vs.	12.5mg ALO/1000mg MET BD	-0.44 [-0.73, -0.16]	
12.5mg ALO BD	vs.	25mg ALO	-0.04 [-0.30, +0.22]	
12.5mg ALO/500mg MET BD	vs.	Placebo	-1.37 [-1.63, -1.11]	
12.5mg ALO/1000mg MET BD	vs.	Placebo	-1.70 [-1.96, -1.45]	

Table 10 Continued. Main efficacy trials (randomised, double blind) with main outcomes; adult patients with poorly controlled T2DM; alogliptin = once daily unless otherwise specified; CFB = change from baseline

Study 305 (N=2638); add-on to metformin; relative efficacy vs. active comparator/MET; 52 weeks; N=1588/2638 = 60%; (ongoing)	HbA1c% (CFB)	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 52 weeks	BW kg (CFB)
12.5mg ALO/MET	-0.62	-0.28	51.5%	-0.64
25.0mg ALO/MET	-0.61	-0.40	55.3%	-0.91
Glipizide/MET	-0.52	0.05	47.4%	0.89
Study 007 (N=500); add-on to a SU; absolute treatment effect in patients on SU; 26 weeks	HbA1c% (CFB) Treatment Difference [95%CI] vs. Placebo	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 26 weeks	BW kg (CFB)
12.5mg ALO/SU	-0.39 [-0.59, -0.19]	-0.26	29.6%	0.60
25.0mg ALO/SU	-0.53 [-0.73, -0.33]	-0.46	34.8%	0.68
Placebo/SU		0.12	18.2%	-0.20
Study 009 (N=493); add-on to a thiazolidinedione; absolute treatment effect in patients on a TZD with or without MET or SU; 26 weeks	HbA1c% (CFB) Treatment Difference [95%CI] vs. Placebo	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 26 weeks	BW kg (CFB)
12.5mg/TZD	-0.47 [-0.67, -0.28]	-1.09	44.2%	1.46
25.0mg/TZD	-0.61 [-0.80, -0.41]	-1.10	49.2%	1.09
Placebo/TZD		-0.32	34.0%	1.04
Study 002 (N=655); add-on to Pioglitazone; relative efficacy; 26 weeks	HbA1c% (CFB)	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 26 weeks	BW kg (CFB)
25.0mg ALO	-0.96	-1.43	24.4%	-0.29
12.5mg ALO/30mg PIO	-1.56	-2.69	53.4%	2.51
25.0mg ALO/30mg PIO	-1.71	-2.79	62.8%	3.14
30mg PIO	-1.15	-2.07	33.7%	2.19
Study 011 (N=390); add-on to insulin; absolute treatment effect in patients on insulin with or without MET; 26 weeks	HbA1c% (CFB) Treatment Difference [95%CI] vs. Placebo	FPG mmol/L (CFB)	Percent ≤ HbA1c7% at 26 weeks	BW kg (CFB)
12.5mg ALO/insulin	-0.51 [-0.72, -0.30]	0.13	8.4%	0.68
25.0mg ALO/insulin	-0.59 [-0.80, -0.37]	-0.65	7.8%	0.60
Placebo/insulin		0.32	0.8%	0.63

Full Analysis Set/Last Observation Carried Forward

Clinical safety

A summary of pooled analysis from controlled Phase II/III studies is presented here. In addition to collection of safety data in efficacy studies, there were 3 primary clinical safety studies (one CV safety outcomes Study 402; 2 Thorough QT Studies 004 and 019). More safety data were available from supporting studies, extensions and longer term studies. (see CER at Attachment of this AusPAR for details).

The cumulative exposure to alogliptin by dose and duration in controlled Phase II/III studies was as follows, indicating an exposure of 1,752 patients to alogliptin for at least 12 months:

Table 11. Cumulative exposure to alogliptin by dose and duration in controlled Phase II/III studies

Exposure	Placebo	Active Comparator	A12.5	A25	All Alogliptin (a)
Controlled Phase 2 and 3 Study Group					
	N=793	N=2257	N=2476	N=3749	N=6354
Duration in days (b)					
Mean (SD)	141.8 (53.80)	247.3 (116.92)	214.4 (101.59)	219.2 (105.55)	214.2 (105.25)
Median (min, max)	179.0 (1, 210)	210.0 (1, 407)	182.0 (1, 402)	183.0 (1, 393)	182.0 (1, 402)
Cumulative exposure (subjects-years) (c)	307.76	1528.22	1453.25	2249.74	3725.98
Number (%) of subjects exposed for (b)					
<6 months	338 (42.6)	471 (20.9)	468 (18.9)	761 (20.3)	1358 (21.4)
≥6 months - <12 months	455 (57.4)	791 (35.0)	1355 (54.7)	1889 (50.4)	3244 (51.1)
≥12 months - <18 months	0	995 (44.1)	653 (26.4)	1099 (29.3)	1752 (27.6)
≥18 months	0	0	0	0	0

A total of 1,144 patients treated with alogliptin were in the age group 65-74 years, 140 in the age group 75-84 years and one aged ≥ 85 years. A total of 1916 alogliptin treated patients had mild renal impairment, 279 with moderate and 2 patients with severe renal impairment.

Adverse events (AEs)

Overall AEs in controlled Phase II/III studies were as follows, indicating similar rates (per 100 Patient-Years (PY)) in alogliptin groupings with respect to rates of AEs, discontinuation, SAEs and deaths compared to placebo and active control grouping:

Table 12. Overview of AEs – Controlled Phase II and III Study Group

	Number (%) of Subjects [Events per 100 Subject-Years]				
Event Type	Placebo N=793	Active Comparator N=2257	A12.5 N=2476	A25 N=3749	All Alogliptin (a) N=6354
Any TEAE	514 (64.8) [438.0]	1548 (68.6) [330.1]	1672 (67.5) [333.2]	2497 (66.6) [342.1]	4234 (66.6) [340.5]
Leading to discontinuation of study drug	18 (2.3) [5.8]	132 (5.8) [8.7]	88 (3.6) [6.5]	155 (4.1) [7.1]	248 (3.9) [7.0]
SAEs	25 (3.2) [9.4]	117 (5.2) [9.9]	100 (4.0) [8.5]	175 (4.7) [9.9]	277 (4.4) [9.3]
Deaths	0	4 (0.2) [0.3]	5 (0.2) [0.3]	4 (0.1) [0.2]	9 (0.1) [0.2]

Source: IAS Table 2.1.1.1a.
(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).

A breakdown of AEs with frequency of ≥ 1% (in any grouping) in controlled Phase II/III studies showed similar rates among the groupings with respect to outcomes such as decreased creatinine clearance, peripheral oedema and hypoglycaemia, among others:

Table 13. AEs with frequency of ≥ 1% (in any grouping) in controlled Phase II/III studies

SOC Preferred Term	Number (%) of Subjects Placebo N=793	Active Comparator N=2257	A12.5 N=2476	A25 N=3749	All Alogliptin (a) N=6354
Any TEAE	**127 (16.0)**	**573 (25.4)**	**506 (20.4)**	**793 (21.2)**	**1314 (20.7)**
Gastrointestinal disorders	**34 (4.3)**	**134 (5.9)**	**136 (5.5)**	**207 (5.5)**	**346 (5.4)**
Diarrhea	12 (1.5)	48 (2.1)	41 (1.7)	50 (1.3)	92 (1.4)
Nausea	8 (1.0)	21 (0.9)	29 (1.2)	47 (1.3)	76 (1.2)
General disorders and administration site conditions	**12 (1.5)**	**93 (4.1)**	**48 (1.9)**	**98 (2.6)**	**148 (2.3)**
Edema peripheral	5 (0.6)	33 (1.5)	16 (0.6)	39 (1.0)	55 (0.9)
Asthenia	0	22 (1.0)	4 (0.2)	17 (0.5)	21 (0.3)
Investigations	**17 (2.1)**	**110 (4.9)**	**101 (4.1)**	**164 (4.4)**	**266 (4.2)**
Creatinine renal clearance decreased	3 (0.4)	22 (1.0)	12 (0.5)	35 (0.9)	47 (0.7)
Metabolism and nutrition disorders	**19 (2.4)**	**146 (6.5)**	**74 (3.0)**	**109 (2.9)**	**183 (2.9)**
Hypoglycemia	0	73 (3.2)	13 (0.5)	9 (0.2)	22 (0.3)
Nervous system disorders	**22 (2.8)**	**95 (4.2)**	**80 (3.2)**	**129 (3.4)**	**216 (3.4)**
Headache	8 (1.0)	28 (1.2)	32 (1.3)	52 (1.4)	88 (1.4)
Dizziness	5 (0.6)	29 (1.3)	21 (0.8)	31 (0.8)	54 (0.8)
Tremor	0	27 (1.2)	6 (0.2)	7 (0.2)	13 (0.2)

Source: IAS Table 2.1.1.25a

(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).

Serious adverse events (SAEs)

In Phase II/III studies 25/793 (3.2%), 117/2257 (5.2%), 100/2476 (4.0%), 175/3749 (4.7%) and 277/6354 (4.4%) patients experienced at least one SAE in placebo, active comparator, alogliptin 12.5 mg, alogliptin 25 mg and alogliptin-overall grouping respectively. SAEs were reported most frequently in cardiac disorder organ system with incidences of 0.4% (placebo), 1.2% (active comparator), 0.8% (alogliptin 12.5 mg) and 1.0% (alogliptin 25 mg). Treatment-related SAEs reported by ≥ 2 patients in any grouping were acute myocardial infarction (2 in active comparator), congestive cardiac failure (3 in 25 mg alogliptin) and, angina unstable, cardiac failure, non-cardiac chest pain, gastroenteritis, and pulmonary embolism (2 patients each in 25 mg alogliptin).

Deaths reported in alogliptin clinical development program

A total of 108 deaths were reported in 55 clinical studies in the alogliptin clinical development program. These included 15 deaths in Phase II/III studies, with five additional deaths pre-treatment. The majority of deaths in Phase II/III were cardiovascular in nature and occurred in 4/2257 (0.2%) patients in active comparator grouping (1 pioglitazone; 3 glipizide) and 9/6354 (0.1%) in alogliptin grouping (5 alogliptin 12.5 mg; 4 alogliptin 25 mg). The mortality rate was similar in active grouping (0.3 deaths/100 PY) versus alogliptin grouping (0.2 deaths/100 PY). This did not include 2 deaths (> 14 days after the last dose) which did not fulfil the definition for inclusion in this analysis.

The CV outcomes Study 402 (T2DM patients with history of Acute Coronary Syndrome; ACS) is an ongoing safety study and reported 44 deaths (26 placebo; 17 alogliptin; 1 treatment-blinded). The long-term extension (4 years) study 012 reported 44 deaths (23 alogliptin 12.5 mg completed; 15 alogliptin 25 mg completed; 6 alogliptin 25 rescued).

Furthermore 5 deaths were reported in Japanese studies (5/1649; 0.3%).

Cardiovascular safety

From the 13 controlled Phase II/III studies, potential CV events were retrospectively adjudicated as Major Adverse Cardiovascular Events (MACE). The occurrence was similar

in alogliptin grouping compared to active comparator for the composite endpoint or its individual components:

Table 14. Primary MACE composite - Controlled Phase II and III Study Group

	Number (%) of Subjects					
	Placebo N=800	Active Comparator N=2267	All Comparators N=3067 (a)	A12.5 N=2483	A25 N=3767	All Alogliptin (b) N=6383
Any MACE	2 (0.3)	14 (0.6)	16 (0.5)	9 (0.4)	16 (0.4)	25 (0.4)
Hazard ratio (All Alogliptin to All Comparators) (c)	--	--	--	--	--	0.806
1-sided 97.5% CI (c)	--	--	--	--	--	(0, 1.511)
CV death	0	3 (0.1)	3 (<0.1)	4 (0.2)	5 (0.1)	9 (0.1)
Nonfatal MI	0	7 (0.3)	7 (0.2)	3 (0.1)	7 (0.2)	10 (0.2)
Nonfatal stroke	2 (0.3)	4 (0.2)	6 (0.2)	2 (<0.1)	4 (0.1)	6 (<0.1)

Source: IAS Table 2.1.5.7a.
(a) The All Comparators Grouping combines Placebo and Active Comparator Groupings.
(b) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).
(c) Time from randomization to the first occurrence of any event adjudicated as a MACE was fitted using a Cox proportional hazards model stratified by study with treatment as a factor.
Note: This table includes all randomized subjects. Subjects are summarized by their randomized treatment assignment.

The interim outcomes from the ongoing CV safety Study 402 were as follows:

Table 15. Primary and secondary MACE composite (402)

	Number (%) of Subjects	
	Placebo N=1076	A25 N=1058
Any primary MACE	46 (4.3)	37 (3.5)
Hazard ratio (Alogliptin to Placebo) (a)	--	0.814
Repeated 1-sided CI (a)	--	0, 1.507
Cardiovascular death	11 (1.0)	11 (1.0)
Nonfatal myocardial infarction	30 (2.8)	21 (2.0)
Nonfatal stroke	5 (0.5)	5 (0.5)
Any secondary MACE	55 (5.1)	41 (3.9)
Hazard ratio (Alogliptin to Placebo) (a)	--	0.750
Repeated 1-sided CI (a)	--	0, 1.332
Cardiovascular death	11 (1.0)	11 (1.0)
Nonfatal myocardial infarction	30 (2.8)	21 (2.0)
Nonfatal stroke	5 (0.5)	5 (0.5)
Urgent revascularization due to unstable angina	9 (0.8)	4 (0.4)

Source: 402 Tables 15.3.3.1.1 and 15.3.3.2.
(a) The hazard ratio was obtained from a CPH model with treatment as the single factor, stratified by geographic region and renal function at Screening. The upper bound is from a repeated 1-sided CI constructed using the group sequential method with an O'Brien-Fleming type spending function designed to preserve an overall 1-sided false-rejection rate of 2.5%.

The hazard ratios (upper limit of 97.5% CI) for the two datasets were as follows:

Table 16. Summary of MACE Analyses

	Hazard Ratio (Alogliptin vs Comparator)	Upper Bound of 1-Sided CI
Primary MACE		
Study 402 (a)	0.814	1.507
Controlled Phase 2 and 3 Study Group (b)	0.806	1.511
Secondary MACE (a) – Study 402	0.750	1.332

Source: IAS Table 2.1.5.7a and Study 402 Tables 15.3.3.1.1 and 15.3.3.2.
(a) The hazard ratio was obtained from a CPH model with treatment as the single factor, stratified by geographic region and renal function at Screening. The upper bound is from a repeated 1-sided CI constructed using the group sequential method with an O'Brien-Fleming-type spending function designed to preserve an overall 1-sided false-rejection rate of 2.5%.
(b) Time from randomization to the first occurrence of any event adjudicated as a MACE was fitted using a Cox proportional hazards model stratified by study with treatment as a factor.

Electrocardiograph

QT prolongation greater than regulatory concern was seen only at supra-therapeutic doses, with multiple dosing in the Thorough QT studies.

Hepatotoxicity

In Phase II/III studies increased ALT was reported for 3 (0.4%) patients in placebo, 13 (0.6%) in active comparator, 15 (0.6%) in alogliptin 12.5g and 14 (0.4%) in alogliptin 25g grouping. The mean change from baseline to end of treatment in liver function tests (LFTs) in Phase II/III trials were as follows:

Table 17. Mean change from baseline to end of treatment in LFTs in Phase II/III trials

	Mean (SD) Change From Baseline to Endpoint				
Parameter	Placebo N=769	Active Comparator N=2257	A12.5 N=2476	A25 N=3702	All Alogliptin (a) N=6307
ALT (U/L)	-0.5 (7.41)	0.2 (31.47)	-0.7 (23.00)	-1.2 (30.49)	-1.0 (27.46)
AST (U/L)	-0.2 (6.47)	0.7 (26.49)	0.0 (14.07)	-0.5 (23.09)	-0.3 (19.77)
Bilirubin, total (µmol/L)	-0.22 (2.887)	-0.30 (3.289)	-0.40 (2.979)	-0.41 (2.989)	-0.40 (2.975)
GGT (U/L)	-0.6 (13.41)	-0.5 (23.90)	-1.2 (18.73)	-1.2 (17.51)	-1.2 (17.89)
ALP (U/L)	-0.3 (10.63)	-1.3 (14.39)	-3.0 (11.96)	-2.9 (11.66)	-2.9 (11.74)
LDH (U/L)	0.6 (16.27)	2.8 (17.12)	2.6 (16.35)	1.5 (16.44)	1.9 (16.35)

Source: IAS Table 3.1.2a.
ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LDH=lactate dehydrogenase.
(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).
Note: Actual number of evaluable subjects may vary slightly from treatment group Ns, as presented in source table.

Acute pancreatitis

Seven cases were reported in Phase II/III studies with alogliptin (0.2 events/100 PY) compared to one in active comparator (0.1 events/100 PY) and no occurrence in the placebo grouping.

Table 18. Incidence of pancreatitis

	Number (%) of Subjects [Events per 100 Subject-Years]				
Preferred Term	Placebo N=793	Active Comparator N=2257	A12.5 N=2476	A25 N=3749	All Alogliptin (a) N=6354
Any Pancreatitis Adverse Event	0	1 (<0.1) [0.1]	2 (<0.1) [0.1]	5 (0.1) [0.3]	7 (0.1) [0.2]
Pancreatitis	0	1 (<0.1) [0.1]	2 (<0.1) [0.1]	3 (<0.1) [0.2]	5 (<0.1) [0.2]
Pancreatitis acute	0	0	0	2 (<0.1) [0.1]	2 (<0.1) [0.1]

Nephrotoxicity

The mean changes in renal function parameters from baseline to end of treatment in Phase II/III studies were as follows and was similar for the two dose levels of alogliptin:

Table 19. Mean changes in renal function parameters from baseline to end of treatment in Phase II/III studies

	Mean (SD) Change From Baseline to Endpoint				
Parameter	Placebo N=769	Active Comparator N=2257	A12.5 N=2476	A25 N=3702	All Alogliptin (a) N=6307
BUN (mmol/L)	0.10 (1.364)	0.19 (1.481)	0.22 (1.438)	0.19 (1.498)	0.21 (1.471)
Serum creatinine (µmol/L)	-0.5 (9.10)	1.9 (10.68)	1.5 (9.84)	1.4 (10.65)	1.4 (10.30)

Source: IAS Table 3.1.2a.
(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).
Note: Actual number of evaluable subjects may vary slightly from treatment group Ns, as presented in source table.

Proportion of patients (%) with markedly abnormal values of renal function parameters was similar between alogliptin groupings, alogliptin dose levels and active comparator but higher than in placebo:

Table 20. Patients with abnormal values of renal function

Parameter (Criterion)	Number (%) of Subjects With ≥1 Markedly Abnormal Result				
	Placebo N=769	Active Comparator N=2257	A12.5 N=2476	A25 N=3702	All Alogliptin (a) N=6307
BUN (>3×ULN)	0	1 (<0.1)	2 (<0.1)	4 (0.1)	6 (<0.1)
Serum creatinine					
>1.5×Baseline	3 (0.4)	42 (1.9)	26 (1.1)	49 (1.3)	75 (1.2)
>1.5×Baseline and >ULN	1 (0.1)	18 (0.8)	12 (0.5)	13 (0.4)	25 (0.4)
>ULN with >26.52 µmol/L increase from Baseline	3 (0.4)	32 (1.4)	28 (1.1)	39 (1.1)	68 (1.1)
≥2×Baseline value	0	10 (0.4)	4 (0.2)	8 (0.2)	12 (0.2)
>176.8 µmol/L	0	9 (0.4)	10 (0.4)	11 (0.3)	21 (0.3)
eGFR					
>25% decrease from Baseline (MDRD)	48 (6.3)	268 (12.0)	243 (9.9)	423 (11.6)	668 (10.7)
>50% decrease from Baseline (MDRD)	0	15 (0.7)	8 (0.3)	12 (0.3)	20 (0.3)
>25% decrease from Baseline (C-G)	31 (4.1)	156 (7.0)	157 (6.4)	256 (7.0)	415 (6.7)
>50% decrease from Baseline (C-G)	0	9 (0.4)	4 (0.2)	8 (0.2)	12 (0.2)

Source: IAS Table 3.3.1a and Table 3.5.1a.
(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).
Note: Actual number of evaluable subjects may vary slightly from group Ns as presented in source table

The incidence of change from baseline in urinalysis parameters in Phase II/III studies was as follows:

Table 21. Change from baseline in urinalysis parameters in Phase II/III studies

Parameter	Change From Baseline to Endpoint				
	Placebo N=769	Active Comparator N=2257	A12.5 N=2476	A25 N=3702	All Alogliptin (a) N=6307
Subjects with Baseline value and at least 1 postbaseline value	n=315	n=392	n=716	n=904	n=1620
Mean (SD) albumin/creatinine ratio	-0.80 (19.212)	-0.02 (17.639)	1.85 (47.607)	1.48 (44.559)	1.64 (45.917)
Median (min,max) albumin/creatinine ratio	-0.10 (-233.6, 69.7)	-0.50 (-102.0, 170.3)	-0.30 (-502.6, 860.4)	-0.50 (-292.5, 1086.7)	-0.40 (-502.6, 1086.7)
Mean (SD) pH	0.04 (0.558)	0.09 (0.573)	0.13 (0.590)	0.11 (0.582)	0.11 (0.584)
Mean (SD) specific gravity	0.0007 (0.00784)	-0.0007 (0.00746)	-0.0009 (0.00702)	-0.0008 (0.00700)	-0.0009 (0.00700)

Source: IAS Table 3.1.3a.
(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).

Hypoglycaemia

The incidence of hypoglycaemia in Phase II/III studies was reported as follows:

Table 22. Incidence of hypoglycaemia in Phase II/III studies

	Number (%) of Subjects				
Episode Category (a)	Placebo N=769	Active Comparator N=2257	A12.5 N=2476	A25 N=3702	All Alogliptin (b) N=6307
Any hypoglycemic episode	48 (6.2)	292 (12.9)	114 (4.6)	135 (3.6)	272 (4.3)
Symptomatic and blood glucose <3.33 mmol/L (Mild to Moderate)	23 (3.0)	205 (9.1)	65 (2.6)	75 (2.0)	144 (2.3)
Symptomatic or asymptomatic and blood glucose <2.78 mmol/L (Mild to Moderate)	18 (2.3)	109 (4.8)	38 (1.5)	43 (1.2)	85 (1.3)
Any episode that requires assistance, associated with a documented blood glucose <3.33 mmol/L (Severe)	3 (0.4)	9 (0.4)	3 (0.1)	4 (0.1)	7 (0.1)

Source: IAS Table 2.1.5.11a.
(a) Subjects may have more than 1 episode per category. In each category summarized, a subject is counted once if the subject reported one or more episode.
(b) The All Alogliptin Grouping combines the 12.5 and 25 mg with the 6.25, 50, and 100 mg groups, which are not shown in the table.
Note: Study 301was excluded from analysis.

Severe cutaneous reactions

The incidence of severe cutaneous reactions in Phase II/III studies was reported as follows:

Table 23. Incidence of severe cutaneous reactions in Phase II/III studies

	Number (%) of Subjects				
Preferred Term	Placebo N=793	Active Comparators N=2257	A12.5 N=2476	A25 N=3749	All Alogliptin (a) N=6354
Any severe cutaneous adverse reaction TEAE	**3 (0.4)**	**3 (0.1)**	**2 (<0.1)**	**3 (<0.1)**	**5 (<0.1)**
Dermatitis bullous	0	1 (<0.1)	2 (<0.1)	0	2 (<0.1)
Dermatitis exfoliative	1 (0.1)	1 (<0.1)	0	2 (<0.1)	2 (<0.1)
Exfoliative rash	0	0	0	1 (<0.1)	1 (<0.1)
Erythema multiforme	1 (0.1)	0	0	0	0
Skin necrosis	0	1 (<0.1)	0	0	0
Toxic skin eruption	1 (0.1)	0	0	0	0

Source: IAS Table 2.1.5.2a.
(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).

Severe hypersensitivity reactions

The incidence of anaphylaxis in controlled Phase II/III studies was as follows:

Table 24. Anaphylaxis reaction - Controlled Phase II and III Study Group

	Number (%) of Subjects				
Criteria Met	Placebo N=793	Active Comparators N=2257	A12.5 N=2476	A25 N=3749	All Alogliptin (a) N=6354
A or (B and C) or (D and (B or C))	0	7 (0.3)	3 (0.1)	9 (0.2)	13 (0.2)
A	0	0	0	0	0
B and C	0	5 (0.2)	3 (0.1)	8 (0.2)	12 (0.2)
D and (B or C)	0	2 (<0.1)	0	1 (<0.1)	1 (<0.1)

Source: IAS Table 2.1.5.5a.
Note: The MedDRA v13.0 'Anaphylactic reaction' SMQ includes preferred terms divided into 4 categories: A (specific terms), B (respiratory distress), C (pruritus, generalized flush, and urticaria) and D (vascular collapse).
(a) Combines the 12.5 and 25 mg groups (already shown in the table) with the 6.25, 50, and 100 mg groups (which are not shown in the table).

Further information from the sponsor

The sponsor's response to the TGA request for further information (see Round 2 assessment in the CER at Attachment 2 of this AusPAR) included a review by an independent hepatic review board (Liver Safety Evaluation Committee; LSEC). All available information (July 2012) on hepatic adverse outcomes (clinical trials and post-

market) including summary of hepatic laboratory data from the clinical database was provided to the LSEC.

Six cases of potential DILI have been reported post-market. The clinical evaluator concluded that additional data supplied by the sponsor, whilst reassuring, do not exclude a potential association between alogliptin and drug induced liver injury.

Clinical evaluator's recommendation

The clinical evaluator supports approval of the following indication:

Add-on combination:

> *Nesina / Vipidia is indicated to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, metformin and a thiazolidinedione, or insulin (with or without metformin).*

Initial combination:

> *Nesina / Vipidia is indicated for use as initial combination with metformin to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control and dual alogliptin and metformin therapy is appropriate.*

The clinical evaluator suggested that the risk of drug induced liver injury requires further review and consideration should be given to deferring the decision on approval pending the decision of the FDA which was yet to be made at the time. The Delegate noted that approval of alogliptin by the FDA had since been given (January 2013).

Risk management plan

The RMP has been updated with respect to the following:

- Hypersensitivity and pancreatitis have been included as identified risks (previously potential risks).
- Hepatotoxicity, peripheral necrotic skin lesions, gastrointestinal disorders and infections have been added as potential risks.
- Malignancies have been added as important missing information (currently concurrent CV disease, severe hepatic disease, severe renal disease/ESRD on dialysis, pregnant or lactating women, children and adolescents).

RMP evaluators advise adoption of RMP version April 2012, including ASA Version July 2012 with any subsequent updates as condition of registration. Addition of hypoglycaemia in combination with suphonylureas or insulin as identified risk remains outstanding. This was also supported by ACSOM.

Previously proposed Drug Utilisation Study and Prescription Events Monitoring Study in Europe are no longer being conducted. The RMP evaluators recommend that the sponsor undertake studies that provide additional pharmacovigilance in the absence of Utilisation Study and Prescription Events Monitoring Study, preferably in Australia. This is also supported by ACSOM.

Risk-benefit analysis

Delegate considerations

Pharmacokinetics/pharmacodynamics

Alogliptin has linear and dose proportional PK with excretion via kidney as unchanged drug. There is a component of active renal excretion. The potential for drug interactions associated with hepatic oxidative enzymes is very low. The Delegate considered that alogliptin PK have been well characterised, including the modelling approach undertaken for population PK. Sponsor's comments have been sought in relation to the PSC observations. However, these are not expected to have significant clinical impact in the presence simple pharmacokinetics.

The DPP-4 inhibition demonstrated in the PD studies supported later investigation of 12.5 mg once daily and 25 mg once daily dosing in clinical efficacy studies. The 12.5 mg twice daily (bid) dosing was also tested in a later clinical study (302) and shown to be equivalent to the 25mg once daily dosing consistent with the results seen in the PD studies.

Dose finding

This was investigated in a 12 week Study 003 (6.25 to 100 mg once daily dosing). The results supported the selection of 25 mg once daily dosing based on effect on HbA1c and Fasting Plasma Glucose (FPG). The 12.5 mg dose was supported based on HbA1c, but inconsistent dose effect was seen with respect to FPG the reason for which is not clear. However, both 12.5 mg and 25 mg once daily dosing regimens were later investigated in clinical efficacy trials.

In general, the subsequent efficacy trials supported the use of 25mg once daily dosing as has been proposed for marketing. However, differentiation from 12.5 mg one daily dosing was not always clear or clinically meaningful. This may be relevant in the case of use in renal impairment. The systemic clearance of alogliptin is reduced roughly by 50% and 75% in moderate and severe renal impairment respectively. Consequently, 12.5 mg and 6.25 mg once daily dosing has been proposed in these two situations, respectively. Given the results of 12.5 mg versus 25 mg dosing seen in clinical studies, the proposed dosing regimen in renal impairment may potentially be high and more hypoglycaemic than required. It may also be relevant to cardiovascular adverse effects.

Efficacy

Placebo-corrected, absolute treatment effect, of alogliptin on change in HbA1c following 26 weeks of treatment was found to be -0.54% (12.5 mg once daily) and -0.57% (25 mg once daily) in the study 010. The differentiation between the two doses was more apart with respect to effect on FPG (-0.57 mmol/L versus -0.91 mmol/L respectively) favouring 25 mg once daily dosing consistent with that seen earlier in the dose finding Study 003.

Satisfactory controlled evidence of efficacy using established endpoints with treatment over 26 weeks was provided for the proposed indication as add-on to metformin (Study 008), add-on to a SU (Study 007) and add-on to a TZD (Studies 009, 002). Longer term controlled (Study 305) or uncontrolled data also available for these. The treatment effect especially with respect to HbA1c was similar to that demonstrated against placebo in study 010 and clinically meaningful. There was no consistent effect on body weight.

The add-on use with insulin was investigated in study 011 in a 26 week study. The number of patients participating in this study was small (insulin/insulin-alogliptin 12.5 mg/insulin-alogliptin 25 mg 51/54/57 and insulin-MET/insulin-MET-alogliptin 12.5 mg/insulin-MET-alogliptin 25 mg 79/77/72 randomised patients, respectively). Furthermore, the treatment effect by way of dose response on HbA1c and FPG was not

consistent. Less than 10% patients achieved HbA1c% below 7% at 26 weeks. There was no effect on body weight. The data are considered not sufficiently convincing. Exposure to greater number of patients in each of subgroups and controlled experience of at least 52 weeks, given the results in the Study 011, may likely provide more robust and reliable estimates of treatment effect appropriate for regulatory purposes.

The proposal to use alogliptin/MET as initial combination is based on the Study 302. This, however, was a supporting study only with small number of patients in each of a number of comparator groups and was not primarily intended to assess initial use. Given also the fact that sufficient safety information for a new chemical agent in post-market phase is not available and the proposed initial use is generally not consistent with the clinical guidelines, this indication is not supported.

Consequently, references to clinical trials in the PI for use with insulin, as initial combination and against placebo (implying prescribing information as monotherapy) will need to be removed from the document.

Safety

Integrated safety data from controlled Phase II/III studies was unremarkable and limited. Well recognised, expected and serious safety concerns with this class of medicine include cardiovascular effects, pancreatitis (some emerging concern about dysplastic pancreatic changes with incretin mimetic drugs) and skin reactions. The reporting 6 cases of severe drug induced hepatic injury in post-market reporting, in association with alogliptin use, has also become a major safety concern. The signal is more likely to be for a propensity for idiosyncratic severe liver reactions rather than cumulative dose related hepatotoxicity, so that active post-market surveillance will be critical.

Publicly available information from approval documents in the US indicates the conclusion reached by the FDA is that spontaneous reporting will not be sufficient to assess signals of serious risks in association with alogliptin use. The specifically imposed post-market commitments include assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotising pancreatitis, and severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson Syndrome) with specialised follow-up required to collect additional information on the events. This enhanced pharmacovigilance is to continue for a period of 5-10 years from approval. Similarly, randomised, double-blind data against placebo is required for assessment of major adverse cardiovascular events. The US regulator appears to have designated an upper limit (UL) of the 2-sided 95% confidence interval for the relative risk (RR) to be below 1.3 for demonstration of cardiovascular safety. This trial will also collect data on hepatotoxicity, hypersensitivity reactions (including severe cutaneous reactions), serious hypoglycaemia, pancreatitis, and renal toxicity. The trial must include at least 200 patients with moderate renal impairment and 100 patients with severe renal impairment treated with alogliptin.

It is noteworthy that the integrated data from Phase II/III studies and the interim data from the CV study 402 noted above indicate UL of RR to be above the proposed 'no effect' limit of 1.3 fold.

The sponsor, in the response to this Overview, was requested to comment on active surveillance obligations in Australia as above and also confirm that the CV trial referred to in FDA approval is the one currently underway (Study 402).

The Delegate endorsed the final recommendations from the RMP evaluators, including that regarding prescription events monitoring in Australia.

With respect to the PI, the Delegate recommended that precautionary use in NYHA class II/III heart failure should be escalated to a contraindication and precaution advised in the presence of history of any heart failure.

Proposed action

Pending advice from the ACPM and the sponsor's response to the Delegate's Overview, the Delegate considered that the supplied data supported the following therapeutic indication, with appropriate post-market commitments and with dosing as proposed by the sponsor:

> *To improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add-on to metformin, a sulphonylurea, a thiazolidinedione, or metformin and a thiazolidinedione.*

The Delegate proposed revisions to product literature, including the PI. Details of these are beyond the scope of the AusPAR.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to additionally request the committee advise on matters raised in the Overview, above, under *Delegate considerations*.

Response from sponsor

Takeda addressed the following items raised during the TGA evaluation:

- Merits of the data supporting the indications as proposed by the sponsor
- RMP, ASA, need for additional pharmacovigilance activities and active surveillance obligations in Australia
- Items raised by PSC, specifically:
  - Clearance versus creatinine clearance
  - P-glycoprotein (P-gp) interactions in relation to more sensitive drugs
  - Absence of data on half-maximal effective concentration (EC50)
  - Dosing regimen in renal impairment

The sponsor also clarified that the statement that "*the integrated data from Phase II/III studies and the interim data from the CV study 402 … indicate UL of RR to be above the proposed 'no effect' limit of 1.3 fold*" is incorrect. The applicable FDA guidance[14] states that if the premarketing application contains clinical data that show that the upper bound of the two-sided 95% confidence interval for the estimated increased risk is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial will generally be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. Takeda had met the applicable endpoint for Phase II/III studies (UL 1.3-1.8) with a post marketing requirement (PMR) to complete Study 402 to meet the 1.3 UL.

Takeda also contended that a contraindication for use in NYHA class II/III heart failure is not warranted.

The remainder of the sponsor's response has not been included in this AusPAR.

[14] Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), December 2008

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Nesina and Vipidia film coated tablets containing 6.25 mg, 12.5 mg or 25 mg of alogliptin (as benzoate) to have an overall positive benefit–risk profile for the indication;

To improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, metformin and a thiazolidinedione, or insulin (with or without metformin)

The ACPM agreed with the Delegate that there is insufficient safety and efficacy data to support the use alogliptin/metformin as initial combination therapy as the proposal is based only on limited numbers of patients in a supporting study for efficacy.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI and Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the *Clinical Trials* and *Precautions* sections of the PI and relevant sections of the CMI to reference the lack of data in patients with heart failure.
- A statement in the *Precautions* section of the PI and relevant sections of the CMI to ensure caution in the use of this agent in patients with estimated GFR < 60 mL/minute.
- A statement in the *Contraindications* section of the PI and relevant sections of the CMI to ensure alogliptin is not used in severe renal impairment.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Nesina and Vipidia film coated tablets containing 6.25, 12.5 or 25 mg alogliptin (as benzoate) indicated for:

> Nesina/Vipidia is indicated to improve glycaemic control in adult patients(≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, insulin (with or without metformin), or in combination with metformin and a thiazolidinedione when dual therapy does not provide adequate glycaemic control.

Specific conditions applying to these therapeutic goods

- The Nesina/Vipidia (alogliptin as benzoate) EU Risk Management Plan (RMP), Version 3.0, submitted to the EMA in March 2013, including Australian specific Annex (Version 2.0) and Risk Management System Changes (Version 1.0 - 3.0), included with

submission PM -2012-01949-3-5, and any subsequent revisions, as agreed with the TGA must be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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