PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

Active substance:	Alogliptin
Product(s) concerned (brand name[s]):	Vipidia
MAH/Applicant name:	Takeda Pharma A/S Dybendal Allé 10 2630 Taastrup Denmark

Data lock point for this module	16 October 2013
Version number of RMP when this module was last updated	7.0

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
GI	gastrointestinal
HbA1c	glycosylated hemoglobin
NYHA	New York Heart Association
PL	package leaflet
SmPC	Summary of Product Characteristics

VI.1 Elements for Summary Tables in the European Public Assessment Report

VI.1.1 Summary Table of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Hypersensitivity reactions Pancreatitis
Important potential risks	Hepatotoxicity Peripheral necrotic skin lesions Gastrointestinal (GI) disorders Infections Pancreatic cancer
Missing information	Patients with severe heart failure (New York Heart Association [NYHA] class IV) Patients requiring renal or peritoneal dialysis Patients with severe hepatic impairment Pregnant or breastfeeding women Children and adolescents Malignancies

VI.1.2 Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the PhV Plan

Not applicable.

VI.1.3 Summary of Postauthorization Efficacy Development Plan

Not applicable.

VI.1.4 Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Hypersensitivity reactions	A contraindication in patients with hypersensitivity to alogliptin or other dipeptidyl peptidase-4 inhibitors is included in section 4.3 of the Summary of Product Characteristics (SmPC). A warning concerning hypersensitivity with alogliptin is also included in section 4.4 of the SmPC and hypersensitivity is included as an adverse drug reaction (ADR) in section 4.8.	None
Pancreatitis	A warning and guidance is provided in section 4.4 of the SmPC. Pancreatitis is also included as an ADR in section 4.8.	None
Important Potential Risks		
Hepatotoxicity	A warning and guidance concerning hepatotoxicity with alogliptin is included in section 4.4 of the SmPC. Hepatotoxicity is also included as an ADR in section 4.8.	None
Peripheral necrotic lesions	None	None
GI disorders	Abdominal pain and gastroesophageal reflux disease are included as ADRs in section 4.8 of the SmPC. No further risk minimization is required.	None
Infections	Upper respiratory tract infection and nasopharyngitis are included as ADRs in section 4.8 of the SmPC. No further risk minimization is required.	None
Pancreatic cancer	None proposed	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Missing Information		
Patients with severe heart failure (NYHA class IV)	Section 4.4 of the SmPC states that there is limited experience of alogliptin use in clinical trials in patients with congestive heart failure of New York Heart Association (NYHA) functional class III and IV. Use is not recommended in patients with NYHA class IV.	None
Patients requiring renal or peritoneal dialysis	Sections 4.2 and 4.4 of the SmPC states that experience of alogliptin use in patients requiring renal dialysis is limited and that alogliptin has not been studied in patients undergoing peritoneal dialysis	None
Patients with severe hepatic impairment	Sections 4.2 and 4.4 of the SmPC states that alogliptin has not been studied in patients with severe hepatic impairment.	None
Pregnant or breastfeeding women	Section 4.6 of the SmPC states that as a precautionary measure, it is preferable to avoid the use of alogliptin during pregnancy and that a decision on whether to discontinue breastfeeding or to discontinue alogliptin therapy should be made taking into account the benefit of breastfeeding for the child and the benefit of alogliptin therapy for the woman.	None
Children and adolescents	Section 4.2 of the SmPC states that the safety and efficacy of alogliptin has not been established in children and adolescents.	None
Malignancies	None	None

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Diabetes is a long term disease that affects large proportions of people across the globe. According to the World Health Organization fact sheet, more than 220 million people worldwide have diabetes [1], and the International Diabetes Federation predicts that more than 37 million people in European countries will be diagnosed with diabetes within the next 20 years [2]. Of significant concern, the average age of onset of diabetes is getting lower meaning that patients will need to take medication for longer and also require more treatment options. It is estimated that more than 4 million deaths every year may be caused by diabetes and diabetes was the main cause of death in Europe in 2008 [2]. Cardiovascular disease (disease affecting the heart and blood vessels) causes half (50%) of all deaths among patients with type 2 diabetes [2] and 10% to 20% of type 2 diabetes patients will die from kidney failure. In addition, health care costs needed to treat these patients continue to rise. In a 2002 study by the Centre for Health Economics (Stockholm) the yearly average cost was estimated at 29 billion Euros [3].

VI.2.2 Summary of Treatment Benefits

Vipidia is used to lower blood sugar levels in adults with type 2 diabetes. Lowering glucose levels decreases the possibility of damage to your eyes, nerves, and kidneys caused by high glucose levels. Vipidia works to increase the levels of insulin in the body after a meal and decrease the amount of sugar in the body. It must be taken together with other antidiabetic medicines such as sulfonylureas (eg, glipizide, tolbutamide, glibenclamide), metformin, and/or thiazolidinediones (eg, pioglitazone) and metformin and/or insulin. Vipidia is taken when your blood sugar cannot be adequately controlled by diet, exercise, and 1 or more of these other oral antidiabetic medicines.

Clinical studies have been completed in more than 14,000 patients with type 2 diabetes. In these studies over 8000 patients were treated with Vipidia. Patients in the studies were already taking 1 or more different diabetes medicines (for example, metformin, a sulfonylurea, pioglitazone, or insulin). Vipidia was compared with a dummy tablet (placebo) or with treatment with another antidiabetic medication. Control of blood sugar over time is measured by a test called the glycosylated hemoglobin (HbA1c). Using this test, studies of Vipidia showed that treatment with Vipidia helped lower blood sugar levels for these patients. Treatment with the recommended daily dose of 25 mg Vipidia lowered blood sugar levels when given by itself or when combined with other diabetic medicines such as, metformin and/or thiazolidinediones, and metformin and/or insulin.

In Study 010 (patients experiencing poor sugar control glycemic control with diet and exercise alone), those patients taking Vipidia 25 mg achieved better improvements in blood sugar control at Week 26 when compared with patients receiving placebo.

In other studies (Study 008, 007,009 and 011) where Vipidia was added on to other anti-diabetic therapies, such as metformin, sulfonylurea, or thiazolidinediones patients receiving Vipidia 25 mg achieved better blood glucose control than those taking placebo. These studies showed

greater reductions in HbA1c level at Week 26 in patients receiving Vipidia 25 mg when compared with those receiving placebo.

In Study 305, Vipidia was as added on to metformin in patients whose blood sugar was not controlled with the metformin alone. These patients had a greater decrease in HbA1c at 104 weeks compared with glipizide.

In Study 004, in patients whose blood sugar was not controlled with metformin and pioglitazone 30 mg, Vipidia was added or the dose of pioglitazone was increased to 45 mg. In this study, the patients who received alogliptin 25 mg as add on to pioglitazone 30 mg showed better improvements in blood sugar control with greater reductions in HbA1c levels at Week 52 when compared with the group in which pioglitazone dose was increased.

VI.2.3 Unknowns Relating to Treatment Benefits

About 85% of the patients in the Vipidia clinical studies were younger than 65 years old and very few (<2%) were over 75 years of age. Most patients studied were white (70%). Over half of the patients included in the studies had some kidney problems (renal impairment) at the start of the studies, but the number of patients with severe kidney disease who have been studied is low. Reductions in blood sugar were similar across different groups of patients including those with kidney disease and those of different age, being male or female, weight, and race. No diabetes agent has been able to show a benefit on lowering major adverse cardiovascular events (death, heart attack or stroke), although a recently completed study showed that risk for these events was not increased by treatment with Vipidia.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Allergic reactions. (Hypersensitivity reactions)	Allergic reactions have been seen with Vipidia since it has been marketed. Allergic reactions can be severe and life-threatening. Symptoms of a serious allergic reaction may include; rash, raised red patches on your skin (hives), swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing, general itching and feeling of heat especially affecting the scalp, mouth, throat, palms of hands and soles of feet (Stevens-Johnson syndrome).	Vipidia treatment should not be started in patients who have had a previous allergic reaction to Vipidia or any of the other ingredients in this medicine or to any other similar medications that that are taken to control blood sugar. If allergic symptoms occur, Vipidia must be stopped.

Risk	What is Known	Preventability
Inflammation of the pancreas (Pancreatitis)	Pancreatitis has been seen with Vipidia since it has been marketed. Pancreatitis can be severe and life-threatening. Severe and persistent pain in the abdomen (stomach area) which might reach through to the back, as well as nausea and vomiting, could be a sign of an inflamed pancreas (pancreatitis).	If pancreatitis is suspected, Vipidia should be stopped; if acute pancreatitis is confirmed, Vipidia therapy should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Important Potential Risks

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
Liver disease (Hepatotoxicity)	There have been liver problems reported in patients treated with Vipidia. Symptoms include nausea or vomiting, stomach pain, unusual or unexplained tiredness, loss of appetite, dark urine, or yellowing of your skin or the whites of the eyes. Patients should be observed closely for possible effect on the liver. Patients with any evidence of liver disease should have their liver enzymes checked and stopping therapy with Vipidia should be considered.
Skin disorders, such as blistering, ulceration or rash (Peripheral necrotic skin lesions)	Administration of some diabetes medicines that work the same way as Vipidia have been associated with skin disorders in animals. Such skin disorders have not been seen with Vipidia.
GI side effects – stomach ache, diarrhea, indigestion, heart burn (GI disorders)	GI side effects may occur in up to 1 in 10 people treated with Vipidia. In most patients the effects were mild and patients did not stop taking the medicine because of the GI effects.
Infections	Infection of the upper airway (upper respiratory tract infection) and inflamed nose with symptoms such as a sore throat, stuffy or blocked nose (nasopharyngitis) may occur in up to 1 in 10 people treated with Vipidia. In most patients the effects were not serious.
Pancreatic cancer	People with diabetes appear to be at higher risk for several common cancer types such as pancreatic cancer than the general population without diabetes. A study has shown that changes to the pancreas similar to those that occur in cancer may occur in patients receiving incretin therapy (medicines that work in a similar way to alogliptin). There is no sign from clinical trials or from use by prescription that patients taking Vipidia are at greater risk of developing pancreatic cancer.

Missing Information

Risk	What is Known
Patients with severe heart failure (severe limitations on activity, patients experience symptoms at rest and are usually bedbound). (patients with severe heart failure NYHA functional class IV)	There is limited information available on the use of Vipidia in patients with severe heart failure therefore its use is not recommended in these patients.
Patients with kidney disease requiring dialysis	There is limited information available on the use of Vipidia in patients with kidney disease that requires dialysis. Vipidia should be used with caution in these patients.
Patients with severely reduced liver function (patients with severe hepatic impairment)	There is no information available on the use of Vipidia in patients with severely reduced liver function therefore its use is not recommended in these patients.
Pregnant and/or breastfeeding women	There is no information available on the use of Vipidia in pregnant and/or breastfeeding women. Vipidia should not be used during pregnancy or breastfeeding unless your doctor advises it is necessary.
Children and adolescents	There is no information available on the use of Vipidia in patients under 18 years of age; therefore, its use is not recommended in this age group.
Cancer (Malignancies)	People with diabetes appear to be at higher risk for several common cancer types than the general population without diabetes. Studies with Vipidia have not shown an increased risk of any cancer.

VI.2.5 Summary of Additional Risk Minimization Measures by Safety Concern

All medicines have an SmPC, which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay (patient friendly) language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The SmPC and the PL for Vipidia can be found in the Vipidia European public assessment report page.

There are no additional risk minimization measures for Vipidia.

VI.2.6 Planned Postauthorization Development Plan

Not applicable.

Studies That Are a Condition of the Marketing Authorization

Not applicable.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
6.0	13 December 2013	Missing information Use of alogliptin in patients with concurrent cardiovascular disease	This has been updated to use of alogliptin in patients with severe heart failure (NYHA class IV). This is because the cardiovascular outcome study (402) has been completed, which provides data on subjects with concurrent cardiovascular disease including patients with moderate heart failure (NYHA class III).
6.0	13 December 2013	Missing information Use of alogliptin in patients with severe renal disease/end-stage renal disease requiring dialysis	This has been updated to patients requiring renal or peritoneal dialysis. This is because the cardiovascular outcome study (402) has been completed, which provides data on subjects with severe renal impairment.

REFERENCES

1. World Health Organization 312. Diabetes Fact Sheet N°312. Published January 2011. http://www.who.int/mediacentre/factsheets/fs312/en/#.
2. OECD. Diabetes Prevalence and Incidence. In: OECD: Health at a Glance: Europe 2010: OECD Publishing; 2010, p. 52-3.
3. Jonsson B. Revealing the cost of Type II diabetes in Europe. Diabetologia 2002;45(7):S5-12.