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

Active substance:	Alogliptin/metformin
Product(s) concerned (brand name[s]):	Vipdomet
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
DPP-4	dipeptidyl peptidase-4
HbA1c	glycosylated hemoglobin
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 Lactic acidosis (a)
Important potential risks	Hepatotoxicity Peripheral necrotic skin lesions Gastrointestinal disorders Infections Pancreatic cancer
Missing information	Patients with severe heart failure (NYHA class IV) (b) Patients requiring renal or peritoneal dialysis (c) Patients with severe hepatic impairment (d) Pregnant or breastfeeding women Children and adolescents Malignancies

(a) Identified risk for metformin.

(b) Missing information for alogliptin. It should be noted that alogliptin/metfornin is contraindicated in patients with cardiac failure.

(c) Missing information for alogliptin. It should be noted that alogliptin/metformin must not be used for use in patients with moderate or severe renal impairment or end-stage renal disease (creatinine clearance <60 mL/min).

(d) Missing information for alogliptin. It should be noted that alogliptin/metformin is contraindicated in patients with hepatic impairment.

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	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	hypersensitivity to alogliptin or other dipeptidyl peptidase-4 (DPP-4) inhibitors is included in section 4.3 of the Summary of Product Characteristics (SmPC). A warning concerning hypersensitivity is also included in section 4.4 of the SmPC and hypersensitivity is included as an adverse drug reaction (ADR) in section 4.8.	
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
Lactic acidosis	A warning and guidance is provided in section 4.4 and 4.5 of the SmPC. Lactic acidosis is also included as an ADR in section 4.8.	None
Important Potential Risks		
Hepatotoxicity	A warning and guidance concerning hepatotoxicity 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
Gastrointestinal 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	None
Important Missing Information		
Patients with severe heart failure (NYHA class IV)*	Section 4.3 of the SmPC states that alogliptin/metformin must not be used in acute or chronic disease which may cause tisuue hypoxia such as cardiac failure.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Patients requiring renal or peritoneal dialysis*	Information and guidance is included in sections 4.2 and 4.4 of the SmPC	None
Patients with severe hepatic impairment*	Sections 4.2 and 4.3 of the SmPC states that alogliptin/metformin must not be used in patients with hepatic impairment. Special warning in patients with severe renal impairment and end-stage renal disease is is provided in section 4.4	None
Pregnant or breastfeeding women	Section 4.6 of the SmPC states that alogliptin/metformin should not be used in pregnancy or breastfeeding.	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

*Missing information for alogliptin

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, healthcare 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

Vipdomet 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. Vipdomet contains 2 different medicines called alogliptin and metformin in 1 tablet. Alogliptin belongs to a group of medicines called DPP-4 inhibitors. Alogliptin works to increase the levels of insulin in the body after a meal and decrease the amount of sugar in the body. Metformin belongs to a group of medicines called biguanides, which also help to lower blood sugar by lowering the amount of sugar made in the liver and helping insulin to work more effectively. Vipdomet is taken when your blood sugar cannot be adequately controlled by diet, exercise and other antidiabetic medicines such as metformin alone; insulin alone; or metformin and pioglitazone taken together.

Clinical studies with Vipdomet have included over 7150 patients with type 2 diabetes, including 4201 patients who have been treated with alogliptin+metformin. In these studies, Vipdomet was shown to lower blood sugar levels, as measured by a blood test known as glycosylated hemoglobin (or HbA1c), which measure blood sugar control over time. Patients entering these studies had blood sugar levels that were not well controlled by their treatment regimen and received alogliptin or another treatment, which could have been a diabetes medication or a pill, with no medication (called a placebo).

In Study SYR-322-MET-008, patients entered the study receiving metformin and had alogliptin or placebo added to their treatment. They had greater improvements in their blood sugar control when treated with alogliptin compared with placebo.

In Study SYR-322-TZD-009, patients entering the study were receiving pioglitazone, either alone or along with other medicines including metformin or another type of diabetes drug known as a sulfonylurea. Patients were treated with alogliptin or a placebo. Greater improvements in blood sugar control were seen with alogliptin compared with placebo.

In Study SYR-322-INS-011, patients entered the study receiving insulin, either alone or with metformin. Greater improvements in blood sugar control were seen with treatment with alogliptin compared with placebo after 26 weeks of treatment.

In Study 01-06-TL-322OPI-004, patients entered the study using pioglitazone 30 mg and metformin. They received either alogliptin 25 mg in addition to their medications or had their pioglitazone increased from 30 mg to 45 mg. Greater improvement in their blood sugar control was seen with the addition of alogliptin 25 mg compared with increasing the dose of pioglitazone from 30 to 45 mg after 26 and 52 weeks of treatment.

In Study SYR322-305, patients entered the study receiving metformin. Vipidia or a medication known as glipizide were added on to the metformin. Greater improvements in blood sugar control were seen for alogliptin.

VI.2.3 Unknowns Relating to Treatment Benefits

About 83% of the patients receiving Vipdomet (alogliptin+metformin) in the clinical studies were younger than 65 years old and very few (<2%) were over 75 years of age. Most patients studied were White (67%). 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 (<0.1%). Reductions in blood sugar were similar across different groups of patients including those with kidney disease and those of different age, males or females, 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 alogliptin.

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 alogliptin (one of the components of Vipdomet) 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)	Vipdomet treatment should not be started in patients who have had a previous allergic reaction to the components of Vipdomet (alogliptin or metformin) or to any of the other ingredients in the medicine or to any other similar medications taken to control blood sugar. If allergic symptoms occur, Vipdomet must be stopped.
Inflammation of the pancreas (Pancreatitis)	Pancreatitis has been seen with alogliptin (one of the components of Vipdomet) since it has been marketed.	If pancreatitis is suspected, Vipdomet should be stopped; if acute pancreatitis is confirmed,

Risk	What is Known	Preventability
	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).	Vipdomet therapy should not be restarted. Caution should be exercised in patients with a history of pancreatitis.
Build up of lactic acid in the blood (lactic acidosis)	Lactic acidosis has occurred in 1 in 10,000 people that have taken metformin (one of the components of Vipdomet). Lactic acidosis is a medical emergency and must be treated in a hospital. It can particularly affect patients whose kidneys are not working properly. Symptoms include some or all of the following: feeling cold or uncomfortable, severe nausea with or without vomiting, unexplained weight loss, or rapid breathing.	Vipidomet treatment should not be started in patients that have risk factors such as poorly controlled diabetes, ketosis, prolonged length of time with no food, excessive alcohol intake, liver problems and any condition associated with low levels of oxygen in the blood. If lactic acidosis is suspected treatment with Vipdomet should be discontinued and the patient should see a doctor immediately

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 alogliptin (one of the components of Vipdomet). 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 Vipdomet 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 Vipdomet have been associated with skin disorders in animals. Such skin disorders have not been seen with Vipdomet.
Gastrointestinal side effects – stomach ache, diarrhea, indigestion, heart burn (Gastrointestinal disorders)	Gastrointestinal side effects may occur in up to 1 in 10 people treated with Vipdomet. In most patients the effects were mild and patients did not stop taking the medicine because of the gastrointestinal 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 Vipdomet. In most patients the effects were not serious.

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
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—one of the components of Vipdomet). There is no sign from clinical trials or from use by prescription that patients taking Vipdomet 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)	Vipdomet should not be used in patients with heart failure (recent heart attack). There is no information available on the use of alogliptin in patients with severe heart failure.
Patients with kidney disease requiring dialysis	Vipdomet should not be used in patients with severe kidney disease. There is limited information available on the use of alogliptin in patients with kidney disease that requires dialysis.
Patients with severely reduced liver function (patients with severe hepatic impairment)	Vipdomet should not be used in patients with reduced liver function There is no information available on the use of alogliptin in patients with severely reduced liver function
Pregnant and/or breastfeeding women	There is no information available on the use of Vipdomet in pregnant and/or breastfeeding women. Vipdomet should not be used during pregnancy or breastfeeding.
Children and adolescents	There is no information available on the use of Vipdomet 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 Vipidomet have not shown an increased risk of any cancer.

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

All medicines have a 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 Vipdomet can be found in the Vipdomet European public assessment report page.

There are no additional risk minimization measures for Vipdomet.

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
7.0	18 June 2014	Missing information Use in patients with severe heart failure (NYHA class IV) Use in patients requiring renal or peritoneal dialysis Use in patients with severe hepatic impairment	Per PRAC comment these safety concerns were re-included as areas of missing information to be consistent with the alogliptin containing products RMPs.
6.0	13 December 2013	Missing information Use in patients with concurrent cardiovascular disease Use in patients with severe renal disease/end-stage renal disease requiring dialysis Use in patients with severe hepatic impairment	Metformin (and therefore alogliptin/metformin) has always been contraindicated in these groups of patients (section 4.3 SmPC), therefore as these patients will not use the alogliptin/metformin fixed-dose combination they have been removed from the Risk Management Plan as missing information as further data will not become available.

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.